949 a| R15.A48 v.5-8 1885-87 w| LCPER c| 1 i| 000054483736 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/13/2005
949 a| R15.A48 v.9-11 1887-88 w| LCPER c| 1 i| 000054483743 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/13/2005
949 a| R15.A48 v.12-14 1889-90 w| LCPER c| 1 i| 000054483750 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/13/2005
949 a| R15.A48 v.15-17 1890-91 w| LCPER c| 1 i| 000054483767 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/14/2005
949 a| R15.A48 v.18-20 1892-93 w| LCPER c| 1 i| 000054483774 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/14/2005
949 a| R15.A48 v.21-22 1893-94 w| LCPER c| 1 i| 000054483781 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/14/2005
949 a| R15.A48 v.23-24 1894-95 w| LCPER c| 1 i| 000054483798 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/14/2005
949 a| R15.A48 v.25-26 1895-96 w| LCPER c| 1 i| 000054483804 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/14/2005
949 a| R15.A48 v.27-28 1896-97 w| LCPER c| 1 i| 000054483811 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/18/2005
949 a| R15.A48 v.29-30 1897-98 w| LCPER c| 1 i| 000054483828 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/18/2005
949 a| R15.A48 v.31-32 1898-99 w| LCPER c| 1 i| 000054483835 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/18/2005
949 a| R15.A48 v.33-34 1899-1900 w| LCPER c| 1 i| 000054483842 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/18/2005
949 a| R15.A48 v.247 1982 w| LCPER c| 1 i| 000054483859 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/18/2005
949 a| R15.A48 v.248 1982 w| LCPER c| 1 i| 000054483866 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/18/2005
949 a| R15.A48 v.249 1983 w| LCPER c| 1 i| 000054483873 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/18/2005
949 a| R15.A48 v.250 1983 w| LCPER c| 1 i| 000054483880 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/18/2005 o| .PUBLIC. Incl. 83rd Report
949 a| R15.A48 v.292 no.9-12 2004 w| LCPER c| 1 i| 000054894600 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 1/27/2005
949 a| R15.A48 v.251 1984 w| LCPER c| 1 i| 000054483897 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/28/2005
949 a| R15.A48 v.252 1984 w| LCPER c| 1 i| 000054483903 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/28/2005 o| .PUBLIC. Incl. 1983-84 Report
949 a| R15.A48 v.253 1985 w| LCPER c| 1 i| 000054483910 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/28/2005
949 a| R15.A48 v.254 1985 w| LCPER c| 1 i| 000054483972 d| 10/1/2019 l| MFILM-NML m| UP-MICRO q| 1 r| Y s| Y t| MICROFORM u| 1/28/2005
949 a| R15.A48 v.255 1986 w| LCPER c| 1 i| 000054483989 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/28/2005
949 a| R15.A48 v.256 1986 w| LCPER c| 1 i| 000054483958 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/28/2005
949 a| R15.A48 v.257 1987 w| LCPER c| 1 i| 000054483934 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/28/2005
949 a| R15.A48 v.258 1987 w| LCPER c| 1 i| 000054483927 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/28/2005
949 a| R15.A48 v.259 1988 w| LCPER c| 1 i| 000054483941 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/28/2005
949 a| R15.A48 v.260 1988 w| LCPER c| 1 i| 000054483965 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/28/2005
949 a| R15.A48 v.261 1989 w| LCPER c| 1 i| 000054483699 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/28/2005
949 a| R15.A48 v.262 1989 w| LCPER c| 1 i| 000054483682 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/28/2005
949 a| R15.A48 v.263 1990 w| LCPER c| 1 i| 000054483705 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/28/2005
949 a| R15.A48 v.264 1990 w| LCPER c| 1 i| 000054483675 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/28/2005 o| .PUBLIC. Incl. Medical education issue
949 a| R15.A48 v.265 1991 w| LCPER c| 1 i| 000054483712 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/28/2005
949 a| R15.A48 v.266 1991 w| LCPER c| 1 i| 000054483668 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/28/2005
949 a| R15.A48 v.267 1992 w| LCPER c| 1 i| 000054483651 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/28/2005
949 a| R15.A48 v.268 1992 w| LCPER c| 1 i| 000054483644 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/28/2005
949 a| R15.A48 v.269 1993 w| LCPER c| 1 i| 000054483637 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/28/2005
949 a| R15.A48 v.270 1993 w| LCPER c| 1 i| 000054484023 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/28/2005
949 a| R15.A48 v.271 1994 w| LCPER c| 1 i| 000054484016 d| 4/16/2009 l| MFILM-NML m| UP-MICRO q| 2 r| Y s| Y t| MICROFORM u| 1/28/2005
949 a| R15.A48 v.272 1994 w| LCPER c| 1 i| 000054484009 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/28/2005
949 a| R15.A48 v.273 1995 w| LCPER c| 1 i| 000054483996 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/28/2005
949 a| R15.A48 v.274 1995 w| LCPER c| 1 i| 000054484030 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/28/2005
949 a| R15.A48 v.275 1996 w| LCPER c| 1 i| 000054484047 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/28/2005
949 a| R15.A48 v.276 1996 w| LCPER c| 1 i| 000054484054 l| MFILM-NML m| UP-MICRO r| Y s| Y t| MICROFORM u| 1/28/2005
949 a| R15.A48 v.292 no.13-16 2004 w| LCPER c| 1 i| 000054840034 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 3/17/2005
949 a| R15.A48 v.292 no.17-20 2004 w| LCPER c| 1 i| 000054844599 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 3/29/2005
949 a| R15.A48 v.293 no.1-4 2005 w| LCPER c| 1 i| 000054990999 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 5/19/2005
949 a| R15.A48 v.292 no.21-24 2004 w| LCPER c| 1 i| 000054991002 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 5/19/2005
949 a| R15.A48 v.293 no.5-8 2005 w| LCPER c| 1 i| 000055005111 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 6/16/2005
949 a| R15.A48 v.293 no.9-12 2005 w| LCPER c| 1 i| 000055025669 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 8/11/2005
949 a| R15.A48 v.293 no.13-16 2005 w| LCPER c| 1 i| 000055030892 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 8/24/2005
949 a| R15.A48 v.293 no.17-20 2005 w| LCPER c| 1 i| 000055035279 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 9/8/2005
949 a| R15.A48 v.293 no.21-24 2005 w| LCPER c| 1 i| 000055051910 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 10/5/2005
949 a| R15.A48 v.294 no.1-4 2005 w| LCPER c| 1 i| 000055052481 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 11/10/2005
949 a| R15.A48 v.294 no.5-8 2005 w| LCPER c| 1 i| 000054953222 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 2/2/2006
949 a| R15.A48 v.294 no.9-12 2005 w| LCPER c| 1 i| 000054955882 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 2/9/2006
949 a| R15.A48 v.294 no.13-16 2005 w| LCPER c| 1 i| 000054961593 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 2/24/2006
949 a| R15.A48 v.294 no.21-24 2005 w| LCPER c| 1 i| 000054974135 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 4/7/2006
949 a| R15.A48 v.295 no.1-4 2006 w| LCPER c| 1 i| 000055110990 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 5/18/2006
949 a| Microfilm w| ASIS c| 1 i| 121006-970001 l| MICROS-HB m| HARRISBURG r| Y s| Y t| MICROFORM u| 6/7/2006
949 a| R15.A48 v.295 no.5-8 2006 w| LCPER c| 1 i| 000055122207 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 6/26/2006
949 a| R15.A48 v.294 no.17-20 2005 w| LCPER c| 1 i| 000055129268 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 7/20/2006
949 a| R15.A48 v.295 no.9-12 2006 w| LCPER c| 1 i| 000055129275 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 7/20/2006

949 a| R15.A48 v.295 no.13-16 2006 w| LCPER c| 1 i| 000055071079 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 9/22/2006
949 a| R15.A48 v.295 no.17-20 2006 w| LCPER c| 1 i| 000055072779 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 9/28/2006
949 a| R15.A48 v.295 no.21-24 2006 w| LCPER c| 1 i| 000055081849 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 11/2/2006
949 a| R15.A48 v.296 no.1-4 2006 w| LCPER c| 1 i| 000055193009 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 2/26/2007
949 a| R15.A48 v.296 no.5-8 2006 w| LCPER c| 1 i| 000055193504 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 3/2/2007
949 a| R15.A48 v.296 no.9-12 .2006 w| LCPER c| 1 i| 000055201025 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 3/21/2007
949 a| R15.A48 v.296 no.13-16 2006 w| LCPER c| 1 i| 000055203814 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 3/26/2007
949 a| R15.A48 v.296 no.17-20 2006 w| LCPER c| 1 i| 000055208659 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 4/23/2007
949 a| R15.A48 v.296 no.21-24 2006 w| LCPER c| 1 i| 000061727182 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 8/23/2007
949 a| R15.A48 v.297 no.1-8 2007 w| LCPER c| 1 i| 000059681922 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 2/8/2008
949 a| R15.A48 v.297 no.9-12 2007 w| LCPER c| 1 i| 000059614999 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 3/7/2008
949 a| R15.A48 v.298 no.13-16 2007 w| LCPER c| 1 i| 000059633099 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 4/18/2008
949 a| R15.A48 v.298 no.17-20 2007 w| LCPER c| 1 i| 000059648352 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 6/6/2008
949 a| R15.A48 v.297 no.13-16 2007 w| LCPER c| 1 i| 000059669821 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 8/26/2008
949 a| R15.A48 v.297 no.17-20 2007 w| LCPER c| 1 i| 000059669814 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 8/26/2008
949 a| R15.A48 v.297 no.21-24 2007 w| LCPER c| 1 i| 000059670094 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 8/26/2008
949 a| R15.A48 v.298 no.1-4 2007 w| LCPER c| 1 i| 000059673231 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 9/19/2008
949 a| R15.A48 v.298 no.5-8 2007 w| LCPER c| 1 i| 000059678380 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 9/29/2008
949 a| R15.A48 v.298 no.9-12 2007 w| LCPER c| 1 i| 000055230155 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 11/20/2008
949 a| R15.A48 v.298 no.21-24 2007 w| LCPER c| 1 i| 000059733379 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 2/18/2009
949 a| R15.A48 v.299 no.1-4 2008 w| LCPER c| 1 i| 000059742425 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 3/23/2009
949 a| R15.A48 v.299 no.5-8 2008 w| LCPER c| 1 i| 000059746560 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 4/20/2009
949 a| R15.A48 v.299 no.9-12 2008 w| LCPER c| 1 i| 000059757023 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 5/8/2009
949 a| R15.A48 v.299 no.13-16 2008 w| LCPER c| 1 i| 000059804505 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 5/29/2009
949 a| R15.A48 v.299 no.17-20 2008 w| LCPER c| 1 i| 000059804680 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 6/11/2009
949 a| R15.A48 v.299 no.21-24 2008 w| LCPER c| 1 i| 000059809944 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 6/29/2009
949 a| R15.A48 v.300 no.1-4 2008 w| LCPER c| 1 i| 000059819424 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 7/13/2009
949 a| R15.A48 v.300 no.5-8 2008 w| LCPER c| 1 i| 000059774808 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 9/9/2009
949 a| R15.A48 v.300 no.9-12 2008 w| LCPER c| 1 i| 000059774792 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 9/9/2009
949 a| R15.A48 v.300 no.13-16 2008 w| LCPER c| 1 i| 000059774686 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 9/9/2009
949 a| R15.A48 v.300 no.17-20 2008 w| LCPER c| 1 i| 000059774679 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 9/9/2009
949 a| R15.A48 v.300 no.21-24 2008 w| LCPER c| 1 i| 000059774662 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 9/9/2009
949 a| R15.A48 v.301 no.1-4 2009 w| LCPER c| 1 i| 000059777212 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 9/16/2009
949 a| R15.A48 v.301 no.5-8 2009 w| LCPER c| 1 i| 000059779766 d| 11/11/2009 e| 11/10/2009 l| PATERNO-4 m| UP-PAT n| 1 r| Y s| Y t| PERIODICAL u| 9/23/2009
949 a| R15.A48 v.301 no.9-12 2009 w| LCPER c| 1 i| 000059790525 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 11/11/2009
949 a| R15.A48 v.301 no.13-16 2009 w| LCPER c| 1 i| 000059790518 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 11/11/2009
949 a| R15.A48 v.301 no.17-20 2009 w| LCPER c| 1 i| 000061840645 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 1/5/2010
949 a| R15.A48 v.301 no.21-24 2009 w| LCPER c| 1 i| 000061842458 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 1/14/2010
949 a| R15.A48 v.302 no.1-4 2009 w| LCPER c| 1 i| 000061847088 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 2/10/2010
949 a| R15.A48 v.302 no.9-12 2009 w| LCPER c| 1 i| 000061872370 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 5/11/2010
949 a| R15.A48 v.302 no.5-8 2009 w| LCPER c| 1 i| 000061869721 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 5/18/2010
949 a| R15.A48 v.302 no.13-16 2009 w| LCPER c| 1 i| 000061882034 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 6/24/2010
949 a| R15.A48 v.302 no.17-20 2009 w| LCPER c| 1 i| 000061889361 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 7/14/2010
949 a| R15.A48 v.302 no.21-24 2009 w| LCPER c| 1 i| 000061889354 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 7/14/2010
949 a| R15.A48 v.303 no.1-4 2010 w| LCPER c| 1 i| 000061893016 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 8/4/2010
949 a| R15.A48 v.303 no.5-8 2010 w| LCPER c| 1 i| 000061917934 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 11/24/2010
949 a| R15.A48 v.303 no.9-12 2010 w| LCPER c| 1 i| 000061807020 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 12/10/2010
949 a| R15.A48 v.303 no.21-24 2010 w| LCPER c| 1 i| 000061819672 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 3/7/2011
949 a| R15.A48 v.304 no.1-4 2010 w| LCPER c| 1 i| 000061819795 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 3/7/2011
949 a| R15.A48 v.303 no.13-16 2010 w| LCPER c| 1 i| 000061819665 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 3/7/2011
949 a| R15.A48 v.303 no.17-20 2010 w| LCPER c| 1 i| 000061819801 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 3/7/2011
949 a| R15.A48 v.304 no.9-12 2010 w| LCPER c| 1 i| 000061827721 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 3/21/2011
949 a| R15.A48 v.304 no.5-8 2010 w| LCPER c| 1 i| 0000618277141 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 3/21/2011
949 a| R15.A48 v.304 no.13-16 2010 w| LCPER c| 1 i| 000061833074 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 4/1/2011
949 a| R15.A48 v.304 no.17-20 2010 w| LCPER c| 1 i| 000059404422 d| 2/23/2016 l| PATERNO-4 m| UP-PAT q| 1 r| Y s| Y t| PERIODICAL u| 5/2/2011
949 a| R15.A48 v.304 no.21-24 2010 w| LCPER c| 1 i| 000059415350 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 6/10/2011
949 a| R15.A48 v.305 no.1-4 2011 w| LCPER c| 1 i| 000059418375 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 6/16/2011
949 a| R15.A48 v.305 no.5-8 2011 w| LCPER c| 1 i| 000059429609 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 8/26/2011
949 a| R15.A48 v.305 no.9-12 2011 w| LCPER c| 1 i| 000059428886 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 9/1/2011
949 a| R15.A48 v.305 no.13-16 2011 w| LCPER c| 1 i| 000059428879 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 9/1/2011
949 a| R15.A48 v.305 no.17-20 2011 w| LCPER c| 1 i| 000059432838 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 9/22/2011
949 a| R15.A48 v.305 no.21-24 2011 w| LCPER c| 1 i| 000059436102 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 10/20/2011
949 a| R15.A48 v.306 no.1-4 2011 w| LCPER c| 1 i| 000059436119 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 10/25/2011
949 a| R15.A48 v.306 no.5-8 2011 w| LCPER c| 1 i| 000059368885 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 1/18/2012
949 a| R15.A48 v.306 no.9-12 2011 w| LCPER c| 1 i| 000059369721 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 1/18/2012

949 a| R15.A48 v.306 no.13-16 2011 w| LCPER c| 1 i| 000059369936 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 1/24/2012
949 a| R15.A48 v.306 no.17-20 2011 w| LCPER c| 1 i| 000059385189 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 4/13/2012
949 a| R15.A48 v.306 no.21-24 2011 w| LCPER c| 1 i| 000059385172 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 4/13/2012
949 a| R15.A48 v.307 no.9-12 2012 w| LCPER c| 1 i| 000059442523 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 8/3/2012
949 a| R15.A48 v.307 no.13-16 2012 w| LCPER c| 1 i| 000059442530 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 8/3/2012
949 a| R15.A48 v.307 no.1-8 2012 w| LCPER c| 1 i| 000059441564 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 8/3/2012
949 a| R15.A48 v.307 no.17-20 2012 w| LCPER c| 1 i| 000059447306 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 9/21/2012
949 a| R15.A48 v.307 no.21-24 2012 w| LCPER c| 1 i| 000059447290 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 9/21/2012
949 a| R15.A48 v.308 no.1-4 2012 w| LCPER c| 1 i| 000059456179 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 11/27/2012
949 a| R15.A48 v.308 no.5-8 2012 w| LCPER c| 1 i| 000059456186 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 11/27/2012
949 a| R15.A48 v.308 no.9-12 2012 w| LCPER c| 1 i| 000059459491 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 1/4/2013
949 a| R15.A48 v.308 no.13-16 2012 w| LCPER c| 1 i| 000059459507 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 1/4/2013
949 a| R15.A48 v.308 no.17-20 2012 w| LCPER c| 1 i| 000059470588 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 3/1/2013
949 a| R15.A48 v.308 no.21-24 2012 w| LCPER c| 1 i| 000059470571 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 3/1/2013
949 a| R15.A48 v.309 no.5-8 2013 w| LCPER c| 1 i| 000059475972 d| 6/5/2013 l| PATERNO-4 m| UP-PAT q| 1 r| Y s| Y t| PERIODICAL u| 3/28/2013
949 a| R15.A48 v.309 no.1-4 2013 w| LCPER c| 1 i| 000059475989 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 3/28/2013
949 a| R15.A48 v.309 no.9-12 2013 w| LCPER c| 1 i| 000059483649 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 5/13/2013
949 a| R15.A48 v.309 no.13-16 2013 w| LCPER c| 1 i| 000059496243 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 7/22/2013
949 a| R15.A48 v.309 no.17-20 2013 w| LCPER c| 1 i| 000059497448 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 8/8/2013
949 a| R15.A48 v.309 no.21-24 2013 w| LCPER c| 1 i| 000059497455 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 8/8/2013
949 a| R15.A48 v.310 no.1-4 2013 w| LCPER c| 1 i| 000059502920 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 10/25/2013
949 a| R15.A48 v.310 no.5-8 2013 w| LCPER c| 1 i| 000059503828 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 10/25/2013
949 a| R15.A48 v.310 no.9-12 2013 w| LCPER c| 1 i| 000059505495 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 11/21/2013
949 a| R15.A48 v.310 no.13-16 2013 w| LCPER c| 1 i| 000059505488 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 11/21/2013
949 a| R15.A48 v.310 no.17-20 2013 w| LCPER c| 1 i| 000059514466 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 1/21/2014
949 a| R15.A48 v.310 no.21-24 2013 w| LCPER c| 1 i| 000059514473 d| 6/29/2014 e| 6/27/2014 l| PATERNO-4 m| UP-PAT n| 3 r| Y s| Y t| PERIODICAL u| 1/21/2014
949 a| R15.A48 v.262 no.9-12 1989 w| LCPER c| 1 i| 000077460226 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 10/13/2014
949 a| R15,A48 v.262 no.17-20 1989 w| LCPER c| 1 i| 000077460233 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 10/13/2014
949 a| R15.A48 v.266 no.21-24 1991 w| LCPER c| 1 i| 000077460240 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 10/13/2014
949 a| R15.A48 v.275 no.21-24 1996 w| LCPER c| 1 i| 000077460257 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 10/13/2014
949 a| R15.A48 v.280 no.5-8 1998 w| LCPER c| 1 i| 000077460264 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 10/13/2014
949 a| R15.A48 v.282 no.21-24 1999 w| LCPER c| 1 i| 000077460271 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 10/13/2014
949 a| R15.A48 v.283 no.13-16 2000 w| LCPER c| 1 i| 000077460288 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 10/13/2014
949 a| R15.A48 v.256 no.1-4 1986 w| LCPER c| 1 i| 000077460332 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 10/16/2014
852 8 a| PSt b| HARRISBURG c| MICROS-HB h| Microfilm
866 0 8| 0 a| v.269(1993)-v.272(1994)
852 0 a| PSt b| UP-PAT c| PATERNO-4 h| R15 i| .A48
866 0 8| 0 a| v.114(1940)-v.310(2013)
852 0 1 a| PSt b| UP-ANNEX c| ANNEX h| R15 i| .A48
866 0 8| 0 a| v.35(1900)-v.113(1939)
868 0 8| 2 a| v.47(1906)-v.53(1909):index
852 8 a| PSt b| HARRISBURG c| PERIOD-HB h| Periodical
866 0 8| 0 a| v.251(1984)-v.272(1994),v.273(1995)-v.294(2005)
852 8 a| PSt b| UP-MICRO c| MFILM-NML h| R15 i| .A48
866 0 8| 0 a| v.1(1883)-v.34(1900), v.247(1982)-v.276(1996)

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JAMA : the journal of the American Medical Association

Additional Titles	JAMA, Some microfilm containers have title: A.M.A. journal, and July 1883-June 1960, Journal of the American Medical Association
Published	Chicago : The Association, 1883-
Physical Description	volumes : illustrations ; 28 cm
Additional Creators	American Medical Association

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Availability

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Penn State Harrisburg (2 items)

Call number	Material	Location
Harrisburg - Microforms - 2nd Floor - In-Library Use: Holdings Summary v.269(1993)-v.272(1994) Harrisburg - Periodicals - 2nd Floor - In-Library Use: Holdings Summary v.251(1984)-v.272(1994),v.273(1995)-v.294(2005)		
Periodical	Bound Journal	Harrisburg - Periodicals - 2nd Floor - In-Library Use
Microfilm	Microfilm, Microfiche, etc.	Harrisburg - Microforms - 2nd Floor - In-Library Use

Microforms Library (Paterno) (43 items)

Call number	Material	Location
2nd Floor Paterno - Microfilm: Holdings Summary v.1(1883)-v.34(1900), v.247(1982)-v.276(1996)		
R15.A48 v.276 1996	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.275 1996	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.274 1995	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.273 1995	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.272 1994	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.271 1994	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.270 1993	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.269 1993	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.268 1992	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.267 1992	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.266 1991	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.265 1991	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.264 1990	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.263 1990	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.262 1989	Microfilm, Microfiche, etc.	Request Scan - Penn State Users

R15.A48 v.261 1989	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.260 1988	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.259 1988	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.258 1987	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.257 1987	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.256 1986	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.255 1986	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.254 1985	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.253 1985	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.252 1984	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.251 1984	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.250 1983	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.249 1983	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.248 1982	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.247 1982	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.33-34 1899-1900	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.31-32 1898-99	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.29-30 1897-98	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.27-28 1896-97	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.25-26 1895-96	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.23-24 1894-95	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.21-22 1893-94	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.18-20 1892-93	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.15-17 1890-91	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.12-14 1889-90	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.9-11 1887-88	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.5-8 1885-87	Microfilm, Microfiche, etc.	Request Scan - Penn State Users
R15.A48 v.1-4 1883-85 & v.1-24 index	Microfilm, Microfiche, etc.	Request Scan - Penn State Users

Pattee Library and Paterno Library Stacks (685 items)

Call number	Material	Location
Paterno - 4th Floor: Holdings Summary v.114(1940)-v.310(2013)		
R15.A48 v.310 no.21-24 2013	Bound Journal	Paterno - 4th Floor
R15.A48 v.310 no.17-20 2013	Bound Journal	Paterno - 4th Floor
R15.A48 v.310 no.13-16 2013	Bound Journal	Paterno - 4th Floor
R15.A48 v.310 no.9-12 2013	Bound Journal	Paterno - 4th Floor
R15.A48 v.310 no.5-8 2013	Bound Journal	Paterno - 4th Floor
R15.A48 v.310 no.1-4 2013	Bound Journal	Paterno - 4th Floor
R15.A48 v.309 no.21-24 2013	Bound Journal	Paterno - 4th Floor
R15.A48 v.309 no.17-20 2013	Bound Journal	Paterno - 4th Floor
R15.A48 v.309 no.13-16 2013	Bound Journal	Paterno - 4th Floor
R15.A48 v.309 no.9-12 2013	Bound Journal	Paterno - 4th Floor
R15.A48 v.309 no.5-8 2013	Bound Journal	Paterno - 4th Floor
R15.A48 v.309 no.1-4 2013	Bound Journal	Paterno - 4th Floor
R15.A48 v.308 no.21-24 2012	Bound Journal	Paterno - 4th Floor
R15.A48 v.308 no.17-20 2012	Bound Journal	Paterno - 4th Floor
R15.A48 v.308 no.13-16 2012	Bound Journal	Paterno - 4th Floor
R15.A48 v.308 no.9-12 2012	Bound Journal	Paterno - 4th Floor

R15.A48 v.308 no.5-8 2012	Bound Journal	Paterno - 4th Floor
R15.A48 v.308 no.1-4 2012	Bound Journal	Paterno - 4th Floor
R15.A48 v.307 no.21-24 2012	Bound Journal	Paterno - 4th Floor
R15.A48 v.307 no.17-20 2012	Bound Journal	Paterno - 4th Floor
R15.A48 v.307 no.13-16 2012	Bound Journal	Paterno - 4th Floor
R15.A48 v.307 no.9-12 2012	Bound Journal	Paterno - 4th Floor
R15.A48 v.307 no.1-8 2012	Bound Journal	Paterno - 4th Floor
R15.A48 v.306 no.21-24 2011	Bound Journal	Paterno - 4th Floor
R15.A48 v.306 no.17-20 2011	Bound Journal	Paterno - 4th Floor
R15.A48 v.306 no.13-16 2011	Bound Journal	Paterno - 4th Floor
R15.A48 v.306 no.9-12 2011	Bound Journal	Paterno - 4th Floor
R15.A48 v.306 no.5-8 2011	Bound Journal	Paterno - 4th Floor
R15.A48 v.306 no.1-4 2011	Bound Journal	Paterno - 4th Floor
R15.A48 v.305 no.21-24 2011	Bound Journal	Paterno - 4th Floor
R15.A48 v.305 no.17-20 2011	Bound Journal	Paterno - 4th Floor
R15.A48 v.305 no.13-16 2011	Bound Journal	Paterno - 4th Floor
R15.A48 v.305 no.9-12 2011	Bound Journal	Paterno - 4th Floor
R15.A48 v.305 no.5-8 2011	Bound Journal	Paterno - 4th Floor
R15.A48 v.305 no.1-4 2011	Bound Journal	Paterno - 4th Floor
R15.A48 v.304 no.21-24 2010	Bound Journal	Paterno - 4th Floor
R15.A48 v.304 no.17-20 2010	Bound Journal	Paterno - 4th Floor
R15.A48 v.304 no.13-16 2010	Bound Journal	Paterno - 4th Floor
R15.A48 v.304 no.9-12 2010	Bound Journal	Paterno - 4th Floor
R15.A48 v.304 no.5-8 2010	Bound Journal	Paterno - 4th Floor
R15.A48 v.304 no.1-4 2010	Bound Journal	Paterno - 4th Floor
R15.A48 v.303 no.21-24 2010	Bound Journal	Paterno - 4th Floor
R15.A48 v.303 no.17-20 2010	Bound Journal	Paterno - 4th Floor
R15.A48 v.303 no.13-16 2010	Bound Journal	Paterno - 4th Floor
R15.A48 v.303 no.9-12 2010	Bound Journal	Paterno - 4th Floor
R15.A48 v.303 no.5-8 2010	Bound Journal	Paterno - 4th Floor
R15.A48 v.303 no.1-4 2010	Bound Journal	Paterno - 4th Floor
R15.A48 v.302 no.21-24 2009	Bound Journal	Paterno - 4th Floor
R15.A48 v.302 no.17-20 2009	Bound Journal	Paterno - 4th Floor
R15.A48 v.302 no.13-16 2009	Bound Journal	Paterno - 4th Floor
R15.A48 v.302 no.9-12 2009	Bound Journal	Paterno - 4th Floor
R15.A48 v.302 no.5-8 2009	Bound Journal	Paterno - 4th Floor
R15.A48 v.302 no.1-4 2009	Bound Journal	Paterno - 4th Floor
R15.A48 v.301 no.21-24 2009	Bound Journal	Paterno - 4th Floor
R15.A48 v.301 no.17-20 2009	Bound Journal	Paterno - 4th Floor
R15.A48 v.301 no.13-16 2009	Bound Journal	Paterno - 4th Floor
R15.A48 v.301 no.9-12 2009	Bound Journal	Paterno - 4th Floor
R15.A48 v.301 no.5-8 2009	Bound Journal	Paterno - 4th Floor
R15.A48 v.301 no.1-4 2009	Bound Journal	Paterno - 4th Floor
R15.A48 v.300 no.21-24 2008	Bound Journal	Paterno - 4th Floor
R15.A48 v.300 no.17-20 2008	Bound Journal	Paterno - 4th Floor
R15.A48 v.300 no.13-16 2008	Bound Journal	Paterno - 4th Floor
R15.A48 v.300 no.9-12 2008	Bound Journal	Paterno - 4th Floor
R15.A48 v.300 no.5-8 2008	Bound Journal	Paterno - 4th Floor
R15.A48 v.300 no.1-4 2008	Bound Journal	Paterno - 4th Floor

R15.A48 v.299 no.21-24 2008	Bound Journal	Paterno - 4th Floor
R15.A48 v.299 no.17-20 2008	Bound Journal	Paterno - 4th Floor
R15.A48 v.299 no.13-16 2008	Bound Journal	Paterno - 4th Floor
R15.A48 v.299 no.9-12 2008	Bound Journal	Paterno - 4th Floor
R15.A48 v.299 no.5-8 2008	Bound Journal	Paterno - 4th Floor
R15.A48 v.299 no.1-4 2008	Bound Journal	Paterno - 4th Floor
R15.A48 v.298 no.21-24 2007	Bound Journal	Paterno - 4th Floor
R15.A48 v.298 no.17-20 2007	Bound Journal	Paterno - 4th Floor
R15.A48 v.298 no.13-16 2007	Bound Journal	Paterno - 4th Floor
R15.A48 v.298 no.9-12 2007	Bound Journal	Paterno - 4th Floor
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R15.A48 v.298 no.1-4 2007	Bound Journal	Paterno - 4th Floor
R15.A48 v.297 no.21-24 2007	Bound Journal	Paterno - 4th Floor
R15.A48 v.297 no.17-20 2007	Bound Journal	Paterno - 4th Floor
R15.A48 v.297 no.13-16 2007	Bound Journal	Paterno - 4th Floor
R15.A48 v.297 no.9-12 2007	Bound Journal	Paterno - 4th Floor
R15.A48 v.297 no.1-8 2007	Bound Journal	Paterno - 4th Floor
R15.A48 v.296 no.21-24 2006	Bound Journal	Paterno - 4th Floor
R15.A48 v.296 no.17-20 2006	Bound Journal	Paterno - 4th Floor
R15.A48 v.296 no.13-16 2006	Bound Journal	Paterno - 4th Floor
R15.A48 v.296 no.9-12 .2006	Bound Journal	Paterno - 4th Floor
R15.A48 v.296 no.5-8 2006	Bound Journal	Paterno - 4th Floor
R15.A48 v.296 no.1-4 2006	Bound Journal	Paterno - 4th Floor
R15.A48 v.295 no.21-24 2006	Bound Journal	Paterno - 4th Floor
R15.A48 v.295 no.17-20 2006	Bound Journal	Paterno - 4th Floor
R15.A48 v.295 no.13-16 2006	Bound Journal	Paterno - 4th Floor
R15.A48 v.295 no.9-12 2006	Bound Journal	Paterno - 4th Floor
R15.A48 v.295 no.5-8 2006	Bound Journal	Paterno - 4th Floor
R15.A48 v.295 no.1-4 2006	Bound Journal	Paterno - 4th Floor
R15.A48 v.294 no.21-24 2005	Bound Journal	Paterno - 4th Floor
R15.A48 v.294 no.17-20 2005	Bound Journal	Paterno - 4th Floor
R15.A48 v.294 no.13-16 2005	Bound Journal	Paterno - 4th Floor
R15.A48 v.294 no.9-12 2005	Bound Journal	Paterno - 4th Floor
R15.A48 v.294 no.5-8 2005	Bound Journal	Checked out
R15.A48 v.294 no.1-4 2005	Bound Journal	Checked out
R15.A48 v.293 no.21-24 2005	Bound Journal	Paterno - 4th Floor
R15.A48 v.293 no.17-20 2005	Bound Journal	Paterno - 4th Floor
R15.A48 v.293 no.13-16 2005	Bound Journal	Paterno - 4th Floor
R15.A48 v.293 no.9-12 2005	Bound Journal	Paterno - 4th Floor
R15.A48 v.293 no.5-8 2005	Bound Journal	Checked out
R15.A48 v.293 no.1-4 2005	Bound Journal	Checked out
R15.A48 v.292 no.21-24 2004	Bound Journal	Paterno - 4th Floor
R15.A48 v.292 no.17-20 2004	Bound Journal	Paterno - 4th Floor
R15.A48 v.292 no.13-16 2004	Bound Journal	Paterno - 4th Floor
R15.A48 v.292 no.9-12 2004	Bound Journal	Paterno - 4th Floor
R15.A48 v.292 no.5-8 2004	Bound Journal	Paterno - 4th Floor
R15.A48 v.292 no.1-4 2004	Bound Journal	Paterno - 4th Floor
R15.A48 v.291 no.21-24 2004	Bound Journal	Paterno - 4th Floor

R15.A48 v.291 no.17-20 2004	Bound Journal	Paterno - 4th Floor
R15.A48 v.291 no.13-16 2004	Bound Journal	Paterno - 4th Floor
R15.A48 v.291 no.9-12 2004	Bound Journal	Paterno - 4th Floor
R15.A48 v.291 no.5-8 2004	Bound Journal	Paterno - 4th Floor
R15.A48 v.291 no.1-4 2004	Bound Journal	Paterno - 4th Floor
R15.A48 v.290 no.21-24 2003	Bound Journal	Paterno - 4th Floor
R15.A48 v.290 no.17-20 2003	Bound Journal	Paterno - 4th Floor
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R15.A48 v.290 no.9-12 2003	Bound Journal	Paterno - 4th Floor
R15.A48 v.290 no.5-8 2003	Bound Journal	Paterno - 4th Floor
R15.A48 v.290 no.1-4 2003	Bound Journal	Paterno - 4th Floor
R15.A48 v.289 no.21-24 2003	Bound Journal	Paterno - 4th Floor
R15.A48 v.289 no.17-20 2003	Bound Journal	Paterno - 4th Floor
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R15.A48 v.289 no.9-12 2003	Bound Journal	Paterno - 4th Floor
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R15.A48 v.288 no.13-16 2002	Bound Journal	Paterno - 4th Floor
R15.A48 v.288 no.9-12 2002	Bound Journal	Paterno - 4th Floor
R15.A48 v.288 no.5-8 2002	Bound Journal	Paterno - 4th Floor
R15.A48 v.288 no.1-4 2002	Bound Journal	Paterno - 4th Floor
R15.A48 v.287 no.21-24 2002	Bound Journal	Paterno - 4th Floor
R15.A48 v.287 no.17-20 2002	Bound Journal	Paterno - 4th Floor
R15.A48 v.287 no.13-16 2002	Bound Journal	Paterno - 4th Floor
R15.A48 v.287 no.9-12 2002	Bound Journal	Paterno - 4th Floor
R15.A48 v.287 no.5-8 2002	Bound Journal	Paterno - 4th Floor
R15.A48 v.287 no.1-4 2002	Bound Journal	Paterno - 4th Floor
R15.A48 v.286 no.21-24 2001	Bound Journal	Paterno - 4th Floor
R15.A48 v.286 no.17-20 2001	Bound Journal	Paterno - 4th Floor
R15.A48 v.286 no.13-16 2001	Bound Journal	Paterno - 4th Floor
R15.A48 v.286 no.9-12 2001	Bound Journal	Paterno - 4th Floor
R15.A48 v.286 no.5-8 2001	Bound Journal	Paterno - 4th Floor
R15.A48 v.286 no.1-4 2001	Bound Journal	Paterno - 4th Floor
R15.A48 v.285 no.21-24 2001	Bound Journal	Paterno - 4th Floor
R15.A48 v.285 no.17-20 2001	Bound Journal	Paterno - 4th Floor
R15.A48 v.285 no.13-16 2001	Bound Journal	Paterno - 4th Floor
R15.A48 v.285 no.9-12 2001	Bound Journal	Paterno - 4th Floor
R15.A48 v.285 no.5-8 2001	Bound Journal	Paterno - 4th Floor
R15.A48 v.285 no.1-4 2001	Bound Journal	Paterno - 4th Floor
R15.A48 v.284 no.21-24 2000	Bound Journal	Paterno - 4th Floor
R15.A48 v.284 no.17-20 2000	Bound Journal	Paterno - 4th Floor
R15.A48 v.284 no.13-16 2000	Bound Journal	Paterno - 4th Floor
R15.A48 v.284 no.9-12 2000	Bound Journal	Paterno - 4th Floor
R15.A48 v.284 no.5-8 2000	Bound Journal	Paterno - 4th Floor
R15.A48 v.284 no.1-4 2000	Bound Journal	Paterno - 4th Floor
R15.A48 v.283 no.21-24 2000	Bound Journal	Paterno - 4th Floor
R15.A48 v.283 no.17-20 2000	Bound Journal	Paterno - 4th Floor

R15.A48 v.283 no.13-16 2000	Bound Journal	Paterno - 4th Floor
R15.A48 v.283 no.9-12 2000	Bound Journal	Paterno - 4th Floor
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R15.A48 v.283 no.1-4 2000	Bound Journal	Paterno - 4th Floor
R15.A48 v.282 no.21-24 1999	Bound Journal	Paterno - 4th Floor
R15.A48 v.282 no.17-20 1999	Bound Journal	Paterno - 4th Floor
R15.A48 v.282 no.13-16 1999	Bound Journal	Paterno - 4th Floor
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R15.A48 v.280 no.9-12 1998	Bound Journal	Paterno - 4th Floor
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R15.A48 v.279 no.21-24 1998	Bound Journal	Paterno - 4th Floor
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R15.A48 v.279 no.13-16 1998	Bound Journal	Paterno - 4th Floor
R15.A48 v.279 no.9-12 1998	Bound Journal	Paterno - 4th Floor
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R15.A48 v.278 no.21-24 1997	Bound Journal	Paterno - 4th Floor
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R15.A48 v.277 no.13-16 1997	Bound Journal	Paterno - 4th Floor
R15.A48 v.277 no.9-12 1997	Bound Journal	Paterno - 4th Floor
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R15.A48 v.262 no.21-24 1989	Bound Journal	Paterno - 4th Floor
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R15.A48 v.259 no.21-24 1988	Bound Journal	Paterno - 4th Floor
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R15.A48 v.259 no.5-8 1988	Bound Journal	Paterno - 4th Floor
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R15.A48 v.258 no.21-24 1987	Bound Journal	Paterno - 4th Floor
R15.A48 v.258 no.17-20 1987	Bound Journal	Paterno - 4th Floor
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R15.A48 v.258 no.9-12 1987	Bound Journal	Paterno - 4th Floor
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R15.A48 v.257 no.21-24 1987	Bound Journal	Paterno - 4th Floor
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R15.A48 v.256 no.21-24 1986	Bound Journal	Paterno - 4th Floor
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R15.A48 v.255 no.21-24 1986	Bound Journal	Paterno - 4th Floor
R15.A48 v.255 no.17-20 1986	Bound Journal	Paterno - 4th Floor
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R15.A48 v.248 no.17-20 1982	Bound Journal	Paterno - 4th Floor
R15.A48 v.248 no.9-16 1982	Bound Journal	Paterno - 4th Floor
R15.A48 v.248 no.1-8 1982	Bound Journal	Paterno - 4th Floor
R15.A48 v.247 no.17-24 1982	Bound Journal	Paterno - 4th Floor
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R15.A48 v.231 no.5-8 1975	Bound Journal	Paterno - 4th Floor
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R15.A48 v.230 no.5-12 1974	Bound Journal	Paterno - 4th Floor
R15.A48 v.230 no.1-4 1974	Bound Journal	Paterno - 4th Floor
R15.A48 v.229 no.10-14 1974	Bound Journal	Paterno - 4th Floor
R15.A48 v.229 no.6-9 1974	Bound Journal	Paterno - 4th Floor
R15.A48 v.229 no.1-5 1974	Bound Journal	Paterno - 4th Floor
R15.A48 v.228 no.10-13 1974	Bound Journal	Paterno - 4th Floor
R15.A48 v.228 no.6-9 1974	Bound Journal	Paterno - 4th Floor
R15.A48 v.228 no.1-5 1974	Bound Journal	Paterno - 4th Floor
R15.A48 v.227 no.9-12 1974	Bound Journal	Paterno - 4th Floor
R15.A48 v.227 no.5-8 1974	Bound Journal	Paterno - 4th Floor
R15.A48 v.227 no.1-4 1974	Bound Journal	Paterno - 4th Floor
R15.A48 v.226 no.10-13 1973	Bound Journal	Paterno - 4th Floor
R15.A48 v.226 no.6-9 1973	Bound Journal	Paterno - 4th Floor
R15.A48 v.226 no.1-5 1973	Bound Journal	Paterno - 4th Floor
R15.A48 v.225 no.10-13 1973	Bound Journal	Paterno - 4th Floor
R15.A48 v.225 no.6-9 1973 & suppl.	Bound Journal	Paterno - 4th Floor
R15.A48 v.225 no.1-5 1973	Bound Journal	Paterno - 4th Floor
R15.A48 v.224 no.10-13 1973	Bound Journal	Paterno - 4th Floor
R15.A48 v.224 no.6-9 1973	Bound Journal	Paterno - 4th Floor
R15.A48 v.224 no.1-5 1973 & suppl.	Bound Journal	Paterno - 4th Floor

R15.A48 v.223 no.10-13 1973	Bound Journal	Paterno - 4th Floor
R15.A48 v.223 no.6-9 1973	Bound Journal	Paterno - 4th Floor
R15.A48 v.223 no.1-5 1973	Bound Journal	Paterno - 4th Floor
R15.A48 v.222 no.10-13 1972	Bound Journal	Paterno - 4th Floor
R15.A48 v.222 no.6-9 1972	Bound Journal	Paterno - 4th Floor
R15.A48 v.222 no.1-5 1972	Bound Journal	Paterno - 4th Floor
R15.A48 v.221 no.10-13 1972	Bound Journal	Paterno - 4th Floor
R15.A48 v.221 no.6-9 1972	Bound Journal	Paterno - 4th Floor
R15.A48 v.221 no.1-5 1972	Bound Journal	Paterno - 4th Floor
R15.A48 v.220 no.10-13 1972	Bound Journal	Paterno - 4th Floor
R15.A48 v.220 no.5-9 1972	Bound Journal	Paterno - 4th Floor
R15.A48 v.220 no.1-4 1972	Bound Journal	Paterno - 4th Floor
R15.A48 v.219 no.10-13 1972	Bound Journal	Paterno - 4th Floor
R15.A48 v.219 no.6-9 1972	Bound Journal	Paterno - 4th Floor
R15.A48 v.219 no.1-5 1972	Bound Journal	Paterno - 4th Floor
R15.A48 v.218 no.10-13 1971	Bound Journal	Paterno - 4th Floor
R15.A48 v.218 no.5-9 1971	Bound Journal	Paterno - 4th Floor
R15.A48 v.218 no.1-4 1971	Bound Journal	Paterno - 4th Floor
R15.A48 v.217 no.10-13 1971	Bound Journal	Paterno - 4th Floor
R15.A48 v.217 no.5-9 1971	Bound Journal	Paterno - 4th Floor
R15.A48 v.217 no.1-4 1971	Bound Journal	Paterno - 4th Floor
R15.A48 v.216 no.10-13 1971	Bound Journal	Paterno - 4th Floor
R15.A48 v.216 no.5-9 1971	Bound Journal	Paterno - 4th Floor
R15.A48 v.216 no.1-4 1971	Bound Journal	Paterno - 4th Floor
R15.A48 v.215 no.9-13 1971	Bound Journal	Paterno - 4th Floor
R15.A48 v.215 no.5-8 1971	Bound Journal	Paterno - 4th Floor
R15.A48 v.215 no.1-4 1971	Bound Journal	Paterno - 4th Floor
R15.A48 v.214 no.10-13 1970	Bound Journal	Paterno - 4th Floor
R15.A48 v.214 no.5-9 1970	Bound Journal	Paterno - 4th Floor
R15.A48 v.214 no.1-4 1970	Bound Journal	Paterno - 4th Floor
R15.A48 v.213 no.10-13 1970	Bound Journal	Paterno - 4th Floor
R15.A48 v.213 no.5-9 1970	Bound Journal	Paterno - 4th Floor
R15.A48 v.213 no.1-4 1970	Bound Journal	Paterno - 4th Floor
R15.A48 v.212 no.9-13 1970	Bound Journal	Paterno - 4th Floor
R15.A48 v.212 no.5-8 1970	Bound Journal	Paterno - 4th Floor
R15.A48 v.212 no.1-4 1970	Bound Journal	Paterno - 4th Floor
R15.A48 v.211-230 1970-74 index	Bound Journal	Paterno - 4th Floor
R15.A48 v.211 no.9-13 1970	Bound Journal	Paterno - 4th Floor
R15.A48 v.211 no.5-8 1970	Bound Journal	Paterno - 4th Floor
R15.A48 v.211 no.1-4 1970	Bound Journal	Paterno - 4th Floor
R15.A48 v.210 no.9-13 1969	Bound Journal	Paterno - 4th Floor
R15.A48 v.210 no.5-8 1969	Bound Journal	Paterno - 4th Floor
R15.A48 v.210 no.1-4 1969	Bound Journal	Paterno - 4th Floor
R15.A48 v.209 no.9-13 1969	Bound Journal	Paterno - 4th Floor
R15.A48 v.209 no.5-8 1969	Bound Journal	Paterno - 4th Floor
R15.A48 v.209 no.1-4 1969	Bound Journal	Paterno - 4th Floor
R15.A48 v.208 no.9-13 1969	Bound Journal	Paterno - 4th Floor
R15.A48 v.208 no.5-8 1969	Bound Journal	Paterno - 4th Floor

R15.A48 v.208 no.1-4 1969	Bound Journal	Paterno - 4th Floor
R15.A48 v.207 no.9-13 1969	Bound Journal	Paterno - 4th Floor
R15.A48 v.207 no.5-8 1969	Bound Journal	Paterno - 4th Floor
R15.A48 v.207 no.1-4 1969	Bound Journal	Paterno - 4th Floor
R15.A48 v.206 no.10-13 1968	Bound Journal	Paterno - 4th Floor
R15.A48 v.206 no.6-9 1968	Bound Journal	Paterno - 4th Floor
R15.A48 v.206 no.1-5 1968	Bound Journal	Paterno - 4th Floor
R15.A48 v.205 no.10-13 1968	Bound Journal	Paterno - 4th Floor
R15.A48 v.205 no.6-9 1968	Bound Journal	Paterno - 4th Floor
R15.A48 v.205 no.1-5 1968	Bound Journal	Paterno - 4th Floor
R15.A48 v.204 no.10-13 1968	Bound Journal	Paterno - 4th Floor
R15.A48 v.204 no.6-9 1968	Bound Journal	Paterno - 4th Floor
R15.A48 v.204 no.1-5 1968	Bound Journal	Paterno - 4th Floor
R15.A48 v.203 no.10-13 1968	Bound Journal	Paterno - 4th Floor
R15.A48 v.203 no.6-9 1968	Bound Journal	Paterno - 4th Floor
R15.A48 v.203 no.1-5 1968	Bound Journal	Paterno - 4th Floor
R15.A48 v.202 no.8-13 1967	Bound Journal	Paterno - 4th Floor
R15.A48 v.202 no.1-7 1967	Bound Journal	Paterno - 4th Floor
R15.A48 v.201 no.8-13 1967	Bound Journal	Paterno - 4th Floor
R15.A48 v.201 no.1-7 1967	Bound Journal	Paterno - 4th Floor
R15.A48 v.200 no.1-6 1967	Bound Journal	Paterno - 4th Floor
R15.A48 v.199 no.8-13 1967	Bound Journal	Paterno - 4th Floor
R15.A48 v.199 no.1-7 1967	Bound Journal	Paterno - 4th Floor
R15.A48 v.198 no.8-13 1966	Bound Journal	Paterno - 4th Floor
R15.A48 v.198 no.1-7 1966	Bound Journal	Paterno - 4th Floor
R15.A48 v.197 no.8-13 1966	Bound Journal	Paterno - 4th Floor
R15.A48 v.197 no.1-7 1966	Bound Journal	Paterno - 4th Floor
R15.A48 v.196 no.7-13 1966	Bound Journal	Paterno - 4th Floor
R15.A48 v.196 no.1-6 1966	Bound Journal	Paterno - 4th Floor
R15.A48 v.195 no.7-13 1966	Bound Journal	Paterno - 4th Floor
R15.A48 v.195 no.1-6 1966	Bound Journal	Paterno - 4th Floor
R15.A48 v.194 no.7-13 1965	Bound Journal	Paterno - 4th Floor
R15.A48 v.194 no.1-6 1965	Bound Journal	Paterno - 4th Floor
R15.A48 v.193 no.7-13 1965	Bound Journal	Paterno - 4th Floor
R15.A48 v.193 no.1-6 1965	Bound Journal	Paterno - 4th Floor
R15.A48 v.192 no.8-13 1965	Bound Journal	Paterno - 4th Floor
R15.A48 v.192 no.1-7 1965	Bound Journal	Paterno - 4th Floor
R15.A48 v.191 no.8-13 1965	Bound Journal	Paterno - 4th Floor
R15.A48 v.191 no.1-7 1965	Bound Journal	Paterno - 4th Floor
R15.A48 v.190 no.8-13 1964	Bound Journal	Paterno - 4th Floor
R15.A48 v.190 no.1-7 1964	Bound Journal	Paterno - 4th Floor
R15.A48 v.189 no.7-13 1964	Bound Journal	Paterno - 4th Floor
R15.A48 v.189 no.1-6 1964	Bound Journal	Paterno - 4th Floor
R15.A48 v.188 no.7-13 1964	Bound Journal	Paterno - 4th Floor
R15.A48 v.188 no.1-6 1964	Bound Journal	Paterno - 4th Floor
R15.A48 v.187 no.8-13 1964	Bound Journal	Paterno - 4th Floor
R15.A48 v.187 no.1-7 1964	Bound Journal	Paterno - 4th Floor
R15.A48 v.186 1963	Bound Journal	Paterno - 4th Floor
R15.A48 v.185 no.7-13 1963	Bound Journal	Paterno - 4th Floor

R15.A48 v.185 no.1-6 1963	Bound Journal	Paterno - 4th Floor
R15.A48 v.184 1963	Bound Journal	Paterno - 4th Floor
R15.A48 v.183 1963	Bound Journal	Paterno - 4th Floor
R15.A48 v.182 1962	Bound Journal	Paterno - 4th Floor
R15.A48 v.181 1962	Bound Journal	Paterno - 4th Floor
R15.A48 v.180 1962	Bound Journal	Paterno - 4th Floor
R15.A48 v.179 1962	Bound Journal	Paterno - 4th Floor
R15.A48 v.178 1961	Bound Journal	Paterno - 4th Floor
R15.A48 v.177 1961	Bound Journal	Paterno - 4th Floor
R15.A48 v.176 1961	Bound Journal	Paterno - 4th Floor
R15.A48 v.175 1961	Bound Journal	Paterno - 4th Floor
R15.A48 v.174 no.1-9 1960	Bound Journal	Paterno - 4th Floor
R15.A48 v.173 no.9-17 1960	Bound Journal	Paterno - 4th Floor
R15.A48 v.173 no.1-8 1960	Bound Journal	Paterno - 4th Floor
R15.A48 v.172 no.10-18 1960	Bound Journal	Paterno - 4th Floor
R15.A48 v.172 no.1-9 1960	Bound Journal	Paterno - 4th Floor
R15.A48 v.171 no.10-17 1959	Bound Journal	Paterno - 4th Floor
R15.A48 v.171 no.1-9 1959	Bound Journal	Paterno - 4th Floor
R15.A48 v.170 no.10-18 1959	Bound Journal	Paterno - 4th Floor
R15.A48 v.170 no.1-9 1959	Bound Journal	Paterno - 4th Floor
R15.A48 v.169 no.10-17 1959	Bound Journal	Paterno - 4th Floor
R15.A48 v.169 no.1-9 1959	Bound Journal	Paterno - 4th Floor
R15.A48 v.168 no.9-17 1958	Bound Journal	Paterno - 4th Floor
R15.A48 v.168 no.5-8 1958	Bound Journal	Paterno - 4th Floor
R15.A48 v.168 no.1-4 1958	Bound Journal	Paterno - 4th Floor
R15.A48 v.167 no.10-18 1958	Bound Journal	Paterno - 4th Floor
R15.A48 v.167 no.1-9 1958	Bound Journal	Paterno - 4th Floor
R15.A48 v.166 no.9-17 1958	Bound Journal	Paterno - 4th Floor
R15.A48 v.166 no.1-8 1958	Bound Journal	Paterno - 4th Floor
R15.A48 v.165 no.9-17 1957	Bound Journal	Paterno - 4th Floor
R15.A48 v.165 no.1-8 1957	Bound Journal	Paterno - 4th Floor
R15.A48 v.164 no.10-18 1957	Bound Journal	Paterno - 4th Floor
R15.A48 v.164 no.1-9 1957	Bound Journal	Paterno - 4th Floor
R15.A48 v.163 no.9-17 1957	Bound Journal	Paterno - 4th Floor
R15.A48 v.163 no.1-8 1957	Bound Journal	Paterno - 4th Floor
R15.A48 v.162 no.10-18 1956	Bound Journal	Paterno - 4th Floor
R15.A48 v.162 no.1-9 1956	Bound Journal	Paterno - 4th Floor
R15.A48 v.161 no.10-17 1956	Bound Journal	Paterno - 4th Floor
R15.A48 v.161 no.1-9 1956	Bound Journal	Paterno - 4th Floor
R15.A48 v.160 no.9-17 1956	Bound Journal	Paterno - 4th Floor
R15.A48 v.160 no.1-8 1956	Bound Journal	Paterno - 4th Floor
R15.A48 v.159 no.10-18 1955	Bound Journal	Paterno - 4th Floor
R15.A48 v.159 no.1-9 1955	Bound Journal	Paterno - 4th Floor
R15.A48 v.158 no.9-17 1955	Bound Journal	Paterno - 4th Floor
R15.A48 v.158 no.1-8 1955	Bound Journal	Paterno - 4th Floor
R15.A48 v.157 no.10-18 1955	Bound Journal	Paterno - 4th Floor
R15.A48 v.157 no.1-9 1955	Bound Journal	Paterno - 4th Floor
R15.A48 v.156 no.10-17 1954	Bound Journal	Paterno - 4th Floor

R15.A48 v.156 no.1-9 1954	Bound Journal	Paterno - 4th Floor
R15.A48 v.155 no.10-18 1954	Bound Journal	Paterno - 4th Floor
R15.A48 v.155 no.1-9 1954	Bound Journal	Paterno - 4th Floor
R15.A48 v.154 no.10-17 1954	Bound Journal	Paterno - 4th Floor
R15.A48 v.154 no.1-9 1954	Bound Journal	Paterno - 4th Floor
R15.A48 v.153 no.10-17 1953	Bound Journal	Paterno - 4th Floor
R15.A48 v.153 no.1-9 1953	Bound Journal	Paterno - 4th Floor
R15.A48 v.152 no.10-18 1953	Bound Journal	Paterno - 4th Floor
R15.A48 v.152 no.1-9 1953	Bound Journal	Paterno - 4th Floor
R15.A48 v.151 no.10-17 1953	Bound Journal	Paterno - 4th Floor
R15.A48 v.151 no.1-9 1953	Bound Journal	Paterno - 4th Floor
R15.A48 v.150 no.9-17 1952	Bound Journal	Paterno - 4th Floor
R15.A48 v.150 no.1-8 1952	Bound Journal	Paterno - 4th Floor
R15.A48 v.149 no.10-18 1952	Bound Journal	Paterno - 4th Floor
R15.A48 v.149 no.1-9 1952	Bound Journal	Paterno - 4th Floor
R15.A48 v.148 no.9-17 1952	Bound Journal	Paterno - 4th Floor
R15.A48 v.148 no.1-8 1952	Bound Journal	Paterno - 4th Floor
R15.A48 v.147 no.10-18 1951	Bound Journal	Paterno - 4th Floor
R15.A48 v.147 no.1-9 1951	Bound Journal	Paterno - 4th Floor
R15.A48 v.146 no.10-17 1951	Bound Journal	Paterno - 4th Floor
R15.A48 v.146 no.1-9 1951	Bound Journal	Paterno - 4th Floor
R15.A48 v.145 no.9-17 1951	Bound Journal	Paterno - 4th Floor
R15.A48 v.145 no.1-8 1951	Bound Journal	Paterno - 4th Floor
R15.A48 v.144 no.10-18 1950	Bound Journal	Paterno - 4th Floor
R15.A48 v.144 no.1-9 1950	Bound Journal	Paterno - 4th Floor
R15.A48 v.143 no.9-17 1950	Bound Journal	Paterno - 4th Floor
R15.A48 v.143 no.1-8 1950	Bound Journal	Paterno - 4th Floor
R15.A48 v.142 no.9-17 1950	Bound Journal	Paterno - 4th Floor
R15.A48 v.142 no.1-8 1950	Bound Journal	Paterno - 4th Floor
R15.A48 v.141 no.10-18 1949	Bound Journal	Paterno - 4th Floor
R15.A48 v.141 no.1-9 1949	Bound Journal	Paterno - 4th Floor
R15.A48 v.140 no.9-17 1949	Bound Journal	Paterno - 4th Floor
R15.A48 v.140 no.1-8 1949	Bound Journal	Paterno - 4th Floor
R15.A48 v.139 no.10-18 1949	Bound Journal	Paterno - 4th Floor
R15.A48 v.139 no.1-9 1949	Bound Journal	Paterno - 4th Floor
R15.A48 v.138 no.10-17 1948	Bound Journal	Paterno - 4th Floor
R15.A48 v.138 no.1-9 1948	Bound Journal	Paterno - 4th Floor
R15.A48 v.137 no.10-18 1948	Bound Journal	Paterno - 4th Floor
R15.A48 v.137 no.1-9 1948	Bound Journal	Paterno - 4th Floor
R15.A48 v.136 no.10-17 1948	Bound Journal	Paterno - 4th Floor
R15.A48 v.136 no.1-9 1948	Bound Journal	Paterno - 4th Floor
R15.A48 v.135 no.9-17 1947	Bound Journal	Paterno - 4th Floor
R15.A48 v.135 no.1-8 1947	Bound Journal	Paterno - 4th Floor
R15.A48 v.134 no.10-17 1947	Bound Journal	Paterno - 4th Floor
R15.A48 v.134 no.1-9 1947	Bound Journal	Paterno - 4th Floor
R15.A48 v.133 no.9-17 1947	Bound Journal	Paterno - 4th Floor
R15.A48 v.133 no.1-8 1947	Bound Journal	Paterno - 4th Floor
R15.A48 v.132 no.9-17 1946	Bound Journal	Paterno - 4th Floor
R15.A48 v.132 no.1-8 1946	Bound Journal	Paterno - 4th Floor

R15.A48 v.131 no.10-18 1946	Bound Journal	Paterno - 4th Floor
R15.A48 v.131 no.1-9 1946	Bound Journal	Paterno - 4th Floor
R15.A48 v.130 no.9-17 1946	Bound Journal	Paterno - 4th Floor
R15.A48 v.130 no.1-8 1946	Bound Journal	Paterno - 4th Floor
R15.A48 v.129 1945	Bound Journal	Paterno - 4th Floor
R15.A48 v.128 no.10-17 1945	Bound Journal	Paterno - 4th Floor
R15.A48 v.128 no.1-9 1945	Bound Journal	Paterno - 4th Floor
R15.A48 v.127 1945	Bound Journal	Paterno - 4th Floor
R15.A48 v.126 no.10-18 1944	Bound Journal	Paterno - 4th Floor
R15.A48 v.126 no.1-9 1944	Bound Journal	Paterno - 4th Floor
R15.A48 v.125 no.9-17 1944	Bound Journal	Paterno - 4th Floor
R15.A48 v.125 no.1-8 1944	Bound Journal	Paterno - 4th Floor
R15.A48 v.124 no.10-18 1944	Bound Journal	Paterno - 4th Floor
R15.A48 v.124 no.1-9 1944	Bound Journal	Paterno - 4th Floor
R15.A48 v.123 no.10-17 1943	Bound Journal	Paterno - 4th Floor
R15.A48 v.123 no.1-9 1943	Bound Journal	Paterno - 4th Floor
R15.A48 v.122 no.10-18 1943	Bound Journal	Paterno - 4th Floor
R15.A48 v.122 no.1-9 1943	Bound Journal	Paterno - 4th Floor
R15.A48 v.121 no.10-17 1943	Bound Journal	Paterno - 4th Floor
R15.A48 v.121 no.1-9 1943	Bound Journal	Paterno - 4th Floor
R15.A48 v.120 no.10-17 1942	Bound Journal	Paterno - 4th Floor
R15.A48 v.120 no.1-9 1942	Bound Journal	Paterno - 4th Floor
R15.A48 v.119 no.10-18 1942	Bound Journal	Paterno - 4th Floor
R15.A48 v.119 no.1-9 1942	Bound Journal	Paterno - 4th Floor
R15.A48 v.118 no.10-18 1942	Bound Journal	Paterno - 4th Floor
R15.A48 v.118 no.1-9 1942	Bound Journal	Paterno - 4th Floor
R15.A48 v.117 no.18-26 1941	Bound Journal	Paterno - 4th Floor
R15.A48 v.117 no.10-17 1941	Bound Journal	Paterno - 4th Floor
R15.A48 v.117 no.1-9 1941	Bound Journal	Paterno - 4th Floor
R15.A48 v.116 no.18-26 1941	Bound Journal	Paterno - 4th Floor
R15.A48 v.116 no.9-17 1941	Bound Journal	Paterno - 4th Floor
R15.A48 v.116 no.1-8 1941	Bound Journal	Paterno - 4th Floor
R15.A48 v.115 no.18-26 1940	Bound Journal	Paterno - 4th Floor
R15.A48 v.115 no.10-17 1940	Bound Journal	Paterno - 4th Floor
R15.A48 v.115 no.1-9 1940	Bound Journal	Paterno - 4th Floor
R15.A48 v.114 no.18-26 1940	Bound Journal	Paterno - 4th Floor
R15.A48 v.114 no.9-17 1940	Bound Journal	Paterno - 4th Floor
R15.A48 v.114 no.1-8 1940	Bound Journal	Paterno - 4th Floor

Library Storage (152 items)

Call number	Material	Location
Annexed Material: Holdings Summary v.35(1900)-v.113(1939) Indexes v.47(1906)-v.53(1909):index		
R15.A48 v.113 no.19-27 1939	Bound Journal	Annexed Material
R15.A48 v.113 no.10-18 1939	Bound Journal	Annexed Material
R15.A48 v.113 no.1-9 1939	Bound Journal	Annexed Material
R15.A48 v.112 no.18-25 1939	Bound Journal	Annexed Material

R15.A48 v.112 no.9-17 1939	Bound Journal	Annexed Material
R15.A48 v.112 no.1-8 1939	Bound Journal	Annexed Material
R15.A48 v.111 no.19-26 1938	Bound Journal	Annexed Material
R15.A48 v.111 no.10-18 1938	Bound Journal	Annexed Material
R15.A48 v.111 no.1-9 1938	Bound Journal	Annexed Material
R15.A48 v.110 no.19-26 1938	Bound Journal	Annexed Material
R15.A48 v.110 no.10-18 1938	Bound Journal	Annexed Material
R15.A48 v.110 no.1-9 1938	Bound Journal	Annexed Material
R15.A48 v.109 no.19-26 1937	Bound Journal	Annexed Material
R15.A48 v.109 no.10-18 1937	Bound Journal	Annexed Material
R15.A48 v.109 no.1-9 1937	Bound Journal	Annexed Material
R15.A48 v.108 no.18-26 1937	Bound Journal	Annexed Material
R15.A48 v.108 no.10-17 1937	Bound Journal	Annexed Material
R15.A48 v.108 no.1-9 1937	Bound Journal	Annexed Material
R15.A48 v.107 no.19-26 1936	Bound Journal	Annexed Material
R15.A48 v.107 no.10-18 1936	Bound Journal	Annexed Material
R15.A48 v.107 no.1-9 1936	Bound Journal	Annexed Material
R15.A48 v.106 no.14-26 1936	Bound Journal	Annexed Material
R15.A48 v.106 no.1-13 1936	Bound Journal	Annexed Material
R15.A48 v.105 no.14-26 1935	Bound Journal	Annexed Material
R15.A48 v.105 no.1-13 1935	Bound Journal	Annexed Material
R15.A48 v.104 no.14-26 1935	Bound Journal	Annexed Material
R15.A48 v.104 no.1-13 1935	Bound Journal	Annexed Material
R15.A48 v.103 no.14-26 1934	Bound Journal	Annexed Material
R15.A48 v.103 no.1-13 1934	Bound Journal	Annexed Material
R15.A48 v.102 no.14-26 1934	Bound Journal	Annexed Material
R15.A48 v.102 no.1-13 1934	Bound Journal	Annexed Material
R15.A48 v.101 no.15-27 1933	Bound Journal	Annexed Material
R15.A48 v.101 no.1-14 1933	Bound Journal	Annexed Material
R15.A48 v.100 no.13-25 1933	Bound Journal	Annexed Material
R15.A48 v.100 no.1-12 1933	Bound Journal	Annexed Material
R15.A48 v.99 no.14-27 1932	Bound Journal	Annexed Material
R15.A48 v.99 no.1-13 1932	Bound Journal	Annexed Material
R15.A48 v.98 no.14-26 1932	Bound Journal	Annexed Material
R15.A48 v.98 no.1-13 1932	Bound Journal	Annexed Material
R15.A48 v.97 no.14-26 1931	Bound Journal	Annexed Material
R15.A48 v.97 no.1-13 1931	Bound Journal	Annexed Material
R15.A48 v.96 no.14-26 1931	Bound Journal	Annexed Material
R15.A48 v.96 no.1-13 1931	Bound Journal	Annexed Material
R15.A48 v.95 no.14-26 1930	Bound Journal	Annexed Material
R15.A48 v.95 no.1-13 1930	Bound Journal	Annexed Material
R15.A48 v.94 no.14-26 1930	Bound Journal	Annexed Material
R15.A48 v.94 no.1-13 1930	Bound Journal	Annexed Material
R15.A48 v.93 no.14-26 1929	Bound Journal	Annexed Material
R15.A48 v.93 no.1-13 1929	Bound Journal	Annexed Material
R15.A48 v.92 no.14-26 1929	Bound Journal	Annexed Material
R15.A48 v.92 no.1-13 1929	Bound Journal	Annexed Material
R15.A48 v.91 no.14-26 1928	Bound Journal	Annexed Material
R15.A48 v.91 no.1-13 1928	Bound Journal	Annexed Material

R15.A48 v.90 no.14-26 1928	Bound Journal	Annexed Material
R15.A48 v.90 no.1-13 1928	Bound Journal	Annexed Material
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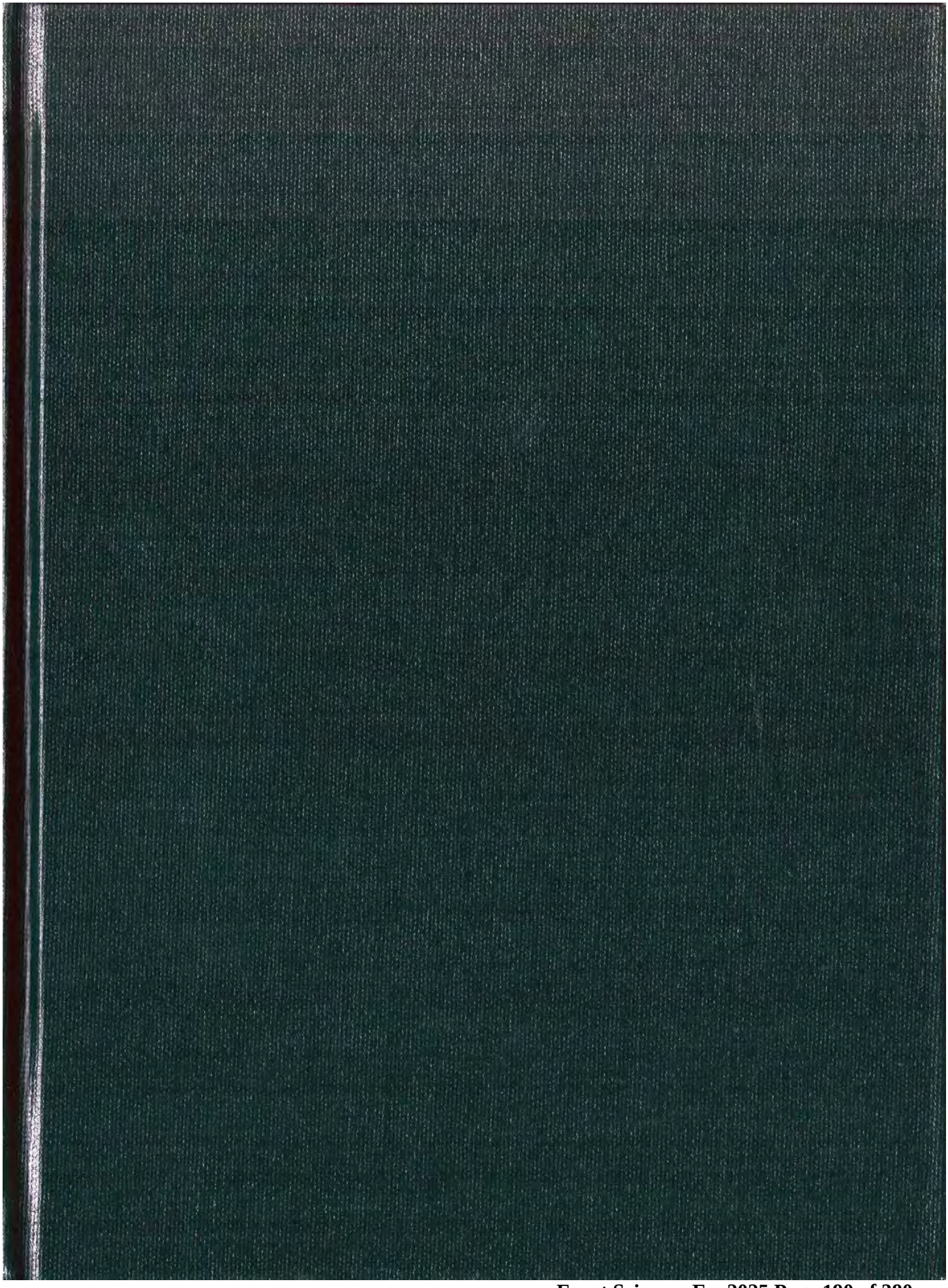
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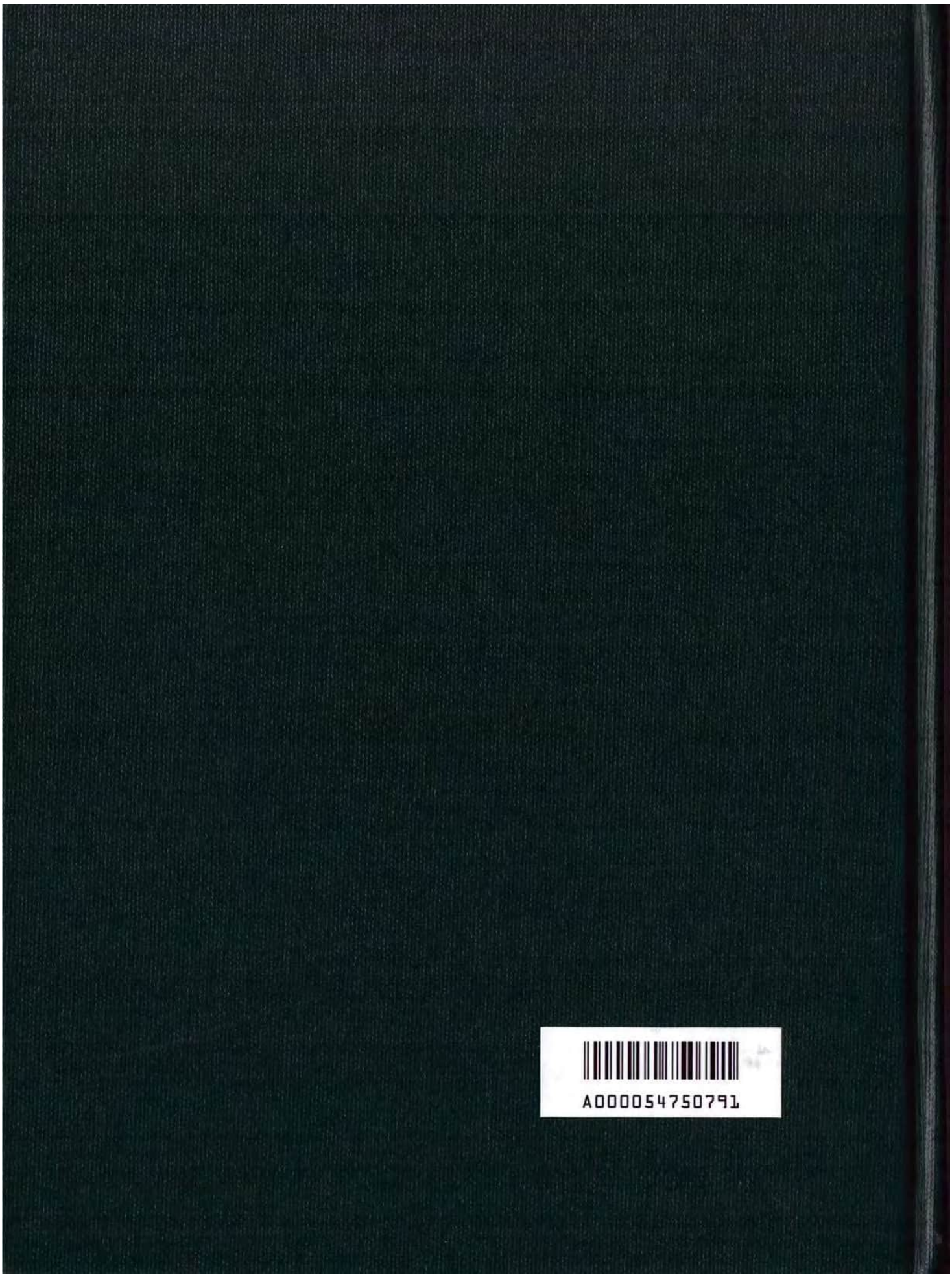
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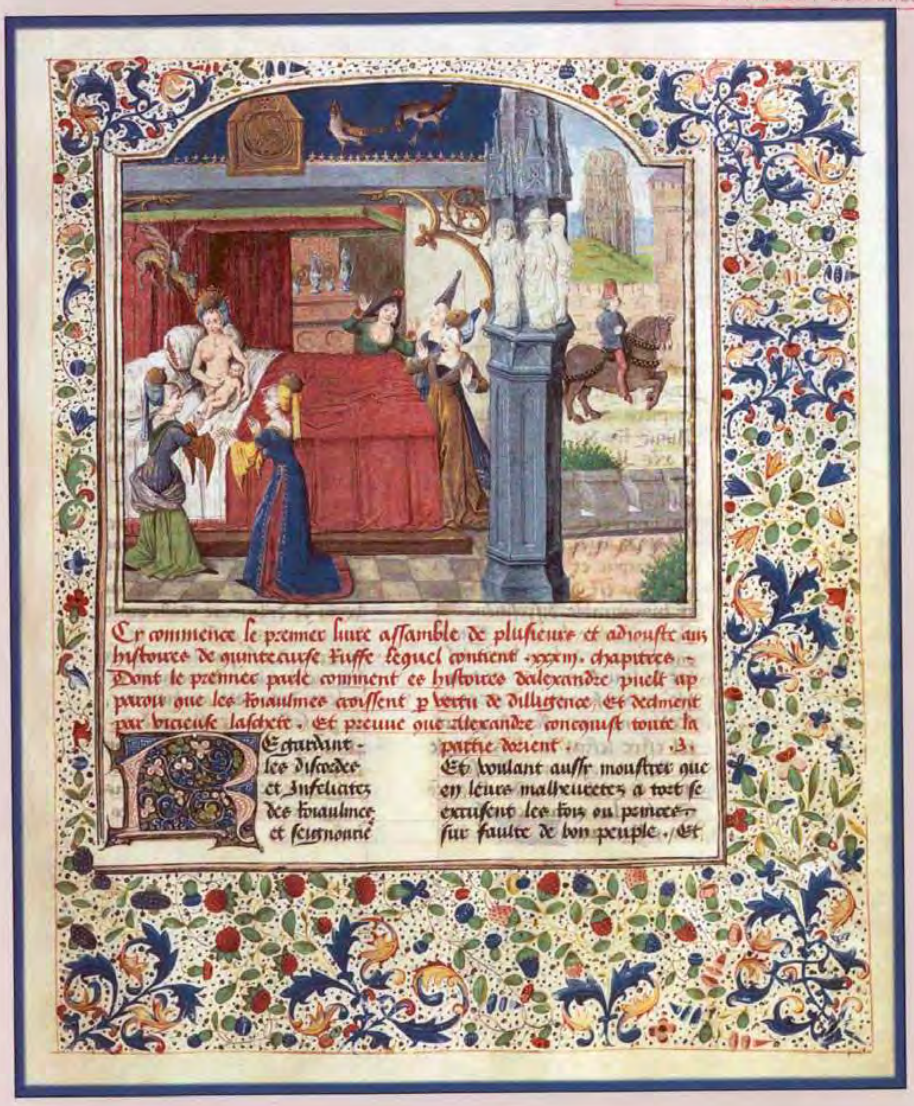
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Computed Tomographic Colonography (Virtual Colonoscopy)

A Multicenter Comparison With Standard Colonoscopy for Detection of Colorectal Neoplasia

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Context Conventional colonoscopy is the best available method for detection of colorectal cancer; however, it is invasive and not without risk. Computed tomographic colonography (CTC), also known as virtual colonoscopy, has been reported to be reasonably accurate in the diagnosis of colorectal neoplasia in studies performed at expert centers.

Objective To assess the accuracy of CTC in a large number of participants across multiple centers.

Design, Setting, and Participants A nonrandomized, evaluator-blinded, noninferiority study design of 615 participants aged 50 years or older who were referred for routine, clinically indicated colonoscopy in 9 major hospital centers between April 17, 2000, and October 3, 2001. The CTC was performed by using multislice scanners immediately before standard colonoscopy; findings at colonoscopy were reported before and after segmental unblinding to the CTC results.

Main Outcome Measures The sensitivity and specificity of CTC and conventional colonoscopy in detecting participants with lesions sized at least 6 mm. Secondary outcomes included detection of all lesions, detection of advanced lesions, possible technical confounders, participant preferences, and evidence for increasing accuracy with experience.

Results A total of 827 lesions were detected in 308 of 600 participants who underwent both procedures; 104 participants had lesions sized at least 6 mm. The sensitivity of CTC for detecting participants with 1 or more lesions sized at least 6 mm was 39.0% (95% confidence interval [CI], 29.6%-48.4%) and for lesions sized at least 10 mm, it was 55.0% (95% CI, 39.9%-70.0%). These results were significantly lower than those for conventional colonoscopy, with sensitivities of 99.0% (95% CI, 97.1%->99.9%) and 100%, respectively. A total of 496 participants were without any lesion sized at least 6 mm. The specificity of CTC and conventional colonoscopy for detecting participants without any lesion sized at least 6 mm was 90.5% (95% CI, 87.9%-93.1%) and 100%, respectively, and without lesions sized at least 10 mm, 96.0% (95% CI, 94.3%-97.6%) and 100%, respectively. Computed tomographic colonography missed 2 of 8 cancers. The accuracy of CTC varied considerably between centers and did not improve as the study progressed. Participants expressed no clear preference for either technique.

Conclusions Computed tomographic colonography by these methods is not yet ready for widespread clinical application. Techniques and training need to be improved.

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COLORECTAL CANCER IS A MAJOR public health issue that has received much attention in recent years. Conventional colonoscopy is widely accepted as the best available method for detection and exclusion of precursor lesions, with the advantage that most can be removed at the same examination.[1,2] However, there is consumer resistance to colonoscopy, which may be perceived as invasive and not without risk. There is a need for simpler screening methods that would allow colonoscopy to be used more selec-

See also p 1772.

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tively and efficiently.[3,4] Computed tomographic colonography (CTC), sometimes called virtual colonoscopy, is a promising candidate.[5-9] Computed tomographic colonography involves helical computed tomographic scanning of the colon after cathartic preparation and colonic distension. Several single-center studies have reported sensitivities of more than 90% for detection of lesions sized 10 mm or more,[10-13] but other studies reported lower data ranging from 61% to 78%.[14-17] The largest recent single-center study reported poor results and considerable variation between readers, with sensitivities of 32%, 34%, and 72%.[18] Although detection (and exclusion) of all lesions is the ultimate goal, the key screening parameter is the ability to detect participants with clinically significant lesions because the detection of any lesion would lead logically to colonoscopy, which should detect nearly all lesions. The definition of a clinically significant lesion is important. Most physicians agree that it is crucial not to miss participants with lesions sized more than 10 mm in diameter and it is desirable to detect all lesions sized more than 6 mm. Studies have reported CTC sensitivities of 85%, 90%, 96%, and 100% for the detection of participants with lesions sized at least 10 mm and sensitivities of 84%, 88%, 93%, and 94% with the threshold at 6 mm.[11,12,14,15] Most of these studies were initiated by committed radiologists, many of them pioneers in the technique, and were restricted to single centers. To be valuable as a screening tool, CTC must perform well in routine practice. Our goal was to assess the accuracy of CTC in a large number of participants across multiple centers. Since this study was completed, good results have been reported from a study conducted in 3 US Armed Services Hospitals.[19]

METHODS

Study Design

The study was a nonrandomized, evaluator-blinded, noninferiority design in which each participant underwent CTC followed up with conventional colonoscopy within 2 hours. Participants aged 50 years or older who were scheduled for a clinically indicated elective conventional colonoscopy were invited to participate. The study did not include a screening population and excluded participants who had undergone colonoscopy within 3 years. Participants were instructed to consume a clear liquid diet (a minimum of 8 oz of liquids every hour) for 24 hours before the CTC examination, and 45 mL of laxative (C. B. Fleet Company Inc, Lynchburg, Va) in 8 oz of cold water. Another 45 mL of the laxative was consumed on the day of the examinations. The radiologist distended the colon with room air or carbon dioxide (by hand pump or automatic insufflator) and obtained a standard computed tomography (CT) scout film to determine adequate bowel distension. Participants were not given oral or intravenous contrast media or smooth muscle relaxants. Imaging was performed by using 2-section and 4-section CT scanners. A nominal slice width of 2.5 mm and a reconstruction increment of 1.5 mm were used for Picker and Siemens software (Picker International Inc, Cleveland, Ohio, and Siemens Medical Solutions, Iselin, NJ). Sites with General Electric (GE Medical Systems, Waukesha, Wis) equipment used a nominal slice thickness of 5.0 mm and a reconstruction increment of 1.0 mm. Complete scans of the colon were performed in the prone and supine positions, each in a single breath hold. Scans were read in 2-dimensional slices, and when necessary by focal 3-dimensional snapshot reconstructions. The radiologists (D.J.V., W.C.S., K.K.K., S.A., C.B., M.A.T., A.R.W., R.B.I., H.B.) recorded their interpretations in 5 sealed envelopes, 1 each for the following colon segments: the rectum and sigmoid, descending colon and splenic flexure, transverse colon and hepatic flexure, ascending colon, and the cecum. Endoscopists were blinded to the CTC results during insertion of the colonoscope. The colon was examined on withdrawal, with the results recorded for each segment. After each segment was examined and the results recorded, the CTC results for that segment were revealed to the endoscopist, allowing immediate reexamination for any discrepancy. This technique of "segmental unblinding" has been used in other studies.[15,19] The radiologists and endoscopists were instructed to record the adequacy of the bowel preparation (presence of fluid or stool) for each colon segment as well as the level of confidence for each detected polyp and each colon segment. Confidence data were recorded as determinate or indeterminate. Full 3-dimensional automated video reconstructions (3-dimensional "fly-throughs") were examined later by the same radiology readers without referring back to their initial 2-dimensional reviews. The 3-dimensional fly-through results were included in the secondary analyses. A preference questionnaire was sent home with each participant with instructions to return the completed form to the clinical center within 48 hours.

The protocol was approved by the institutional review board at each participating center, and all participants provided written informed consent. An independent data and safety monitoring committee was assembled to review participant safety and progress of the study.

Criterion Standard

The criterion standard for the diagnosis of lesions was defined as a combination of the initial findings of conventional colonoscopy, any additional findings on conventional colonoscopy after segmental unblinding to the CTC reports, and the results of additional diagnostic tests performed at a later date when clinically indicated. This means that the positive predictive value for conventional colonoscopy was 100% by definition. Lesion size was defined by measurement of any removed lesion (before fixation) or, if the polyp was not retrieved, by comparison with biopsy forceps during colonoscopy. The data from each participant were reviewed by 2 independent evaluators (V.L.D., Y.Y.P.) by using a matching algorithm, depending on the size and location of each identified lesion. Le-

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sions found at CTC and conventional colonoscopy were considered to be the same lesion (ie, true matches) if their sizes agreed within 50% and if they were in the same or adjacent segments.

Setting

Nine clinical centers (8 in the United States and 1 in England) were recruited in which there were gastroenterologists and radiologists who agreed to collaborate in the study. Each center was limited to 3 named endoscopists and 2 radiologists. Radiologists were required to have performed at least 10 CTC procedures. Optical disks of 5 of their examinations performed according to protocol procedures were mailed to a central panel of radiologists for review of image quality, not diagnostic accuracy, before starting the study.

Outcome Measures

The primary outcome measure was the sensitivity and specificity of CTC (ie, the initial radiologist's report, without any later fly-through data) and conventional colonoscopy in identifying participants with and without lesions sized at least 6 mm.

Secondary outcome measures included the correct detection rate for lesions of any size for CTC and conventional colonoscopy, the detection of advanced lesions, the positive and negative predictive values for CTC and conventional colonoscopy, fly-through data, effect of increasing experience with reading the CTC images, and participant preferences for CTC vs conventional colonoscopy.

Statistical Considerations

The goal of the study was to assess whether the differences between the sensitivity and specificity of CTC and conventional colonoscopy in the detection of colorectal lesions were small enough to use CTC as a tool for the diagnosis of colorectal lesions. Because both CTC and conventional colonoscopy were performed on the same participant, McNemar paired-sample test approach was used for the calculation of the sample size.[20,21] Assuming the sensitivity (and specificity) of conventional colonoscopy was 95% (and 98%) for identifying participants with (and without) at least 1 lesion sized at least 6 mm, 248 participants with at least 1 lesion sized at least 6 mm were necessary to assess the sensitivity of the CTC (power=90%). Approximately 160 participants were required to assess the specificity of CTC. Assuming a 6-mm or more lesion prevalence of 25% and a dropout rate of 5%, approximately 1050 participants were required for enrollment.

The data were processed, managed, and analyzed by the Clinical Innovation Group. Statistical analyses were conducted using SAS version 8.2 (SAS Institute, Cary, NC).

RESULTS

Recruitment was slower than expected. For this reason, the study was stopped after 615 participants were enrolled between April 17, 2000, and October 3, 2001. Mean (SD) age of the participants was 61 years (8.34 years); 45% were men, 87% were white, and 13.5% had a history of colon polyps. Reasons for colonoscopy included overt and occult rectal bleeding, change in stool habit, abdominal pain, and surveillance after polypectomy. Six hundred three participants underwent CTC, 602 had conventional colonoscopy, and 600 had both procedures. Recruitment varied widely between centers, from 10 to 188 participants per center.

Lesions

By the criterion standard, a total of 827 true lesions were detected. In order of frequency, these lesions were found in the sigmoid colon (30.7%), rectum (17.2%), ascending colon (17.2%), transverse (10.5%), descending (9.9%), cecum (7.5%), hepatic flexure (5.3%), and splenic flexure (1.7%). The lesions were detected in 308 participants (51%), varying from 1 to 20 lesions per participant. Of the total 827 lesions, 654 (79.1%) were 1 to 5 mm, 119 (14.4%) were 6 to 9 mm, and 54 (6.5%) were at least 10 mm. There were 29 advanced lesions of more than 6 mm in diameter (19 adenomas with villous features, 2 with high-grade dysplasia, and 8 cancers).

Primary Outcome

One hundred four participants had at least 1 lesion sized at least 6 mm. The CTC identified 41 of these participants (sensitivity, 39.0%; 95% CI, 29.6%-48.4%), whereas conventional colonoscopy identified 103 (sensitivity, 99.0%; 95% CI, 97.1%->99.9%). Four hundred ninety-six participants were without any lesion sized at least 6 mm. The CTC identified 449 of these participants (specificity, 90.5%; 95% CI, 87.9%-93.1%), whereas conventional colonoscopy identified all of them (specificity, 100%).

Secondary Outcomes

The sensitivity and specificity of CTC and conventional colonoscopy for detecting participants with lesions were assessed also for other lesion sizes (TABLE 1). The sensitivity of CTC for detecting participants with lesions sized at least 10 mm was 55.0% (95% CI, 39.9%-70.0%), substantially less than conventional colonoscopy (sensitivity, 100%). For detecting participants without lesions sized at least 10 mm, the specificity for CTC was 96.0% (95% CI, 94.3%-97.6%) and 100% for conventional colonoscopy. The sensitivity of CTC for detecting participants with advanced lesions was 64%; 2 of 8 cancers were missed (a 17-mm lesion in the rectum and a 7-mm lesion in the ascending colon).

Colonoscopy reached the cecum in 98.5% of participants. The CTC and initial conventional colonoscopy examinations both failed to detect 2 large lesions (2.0 cm in the transverse colon and 4.3 cm in the rectum, which were both found by surgery); both of these patients had other lesions sized at least 10 mm that were detected by conventional colonoscopy. Conventional colonoscopy also missed one 7-mm lesion in the sigmoid colon and 19 lesions of 1 to 5 mm. In 95 participants (16%), immediate endoscopic evaluation was needed after opening the envelope with

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Table 1. Detection of Participants With and Without Lesions*

True Lesion Size, mm	Total No. of Participants With Lesions	Initial Conventional Colonoscopy		Computed Tomographic Colonography	
		No. of Participants With Detected Lesions	Sensitivity, % (95% CI)	No. of Participants With Detected Lesions	Sensitivity, % (95% CI)
≥6†	104	103	99.0 (97.1->99.9)	41	39.0 (29.6-48.4)
≥10	42	42	100	23	55.0 (39.9-70.0)
6-9	76	75	98.6 (95.9->99.9)	23	30.0 (19.7-40.3)
1-5	274	265	96.7 (94.6-98.8)	37	13.5 (9.5-17.5)
True Lesion Size, mm	**Total No. of Participants Without Lesions**	**Initial Conventional Colonoscopy**		**Computed Tomographic Colonography**	
		No. of Participants Without Detected Lesions	**Specificity, % (95% CI)**	**No. of Participants Without Detected Lesions**	**Specificity, % (95% CI)**
≥6†	496	496	100	449	90.5 (87.9-93.1)
≥10	558	558	100	535	96.0 (94.3-97.6)
6-9	524	524	100	488	93.1 (90.9-95.2)
1-5	326	326	100	295	90.5 (87.3-93.7)

Abbreviation: CI, confidence interval.
*Participants with multiple lesions are represented in more than 1 size category.
†Primary outcome.

Table 2. Detection of Individual Lesions

True Lesion Size, mm	Criterion Standard (No. of Lesions)	Initial Conventional Colonoscopy		Computed Tomographic Colonography	
		No. of Detected Lesions	Sensitivity, % (95% CI)	No. of Detected Lesions	Sensitivity, % (95% CI)
≥6	173	170	98.0 (95.9->99.9)	55	32.0 (25.0-38.9)
≥10	54	52	96.0 (90.8->99.9)	28	52.0 (38.7-65.3)
6-9	119	118	99.0 (97.2->99.9)	27	22.7 (15.2-30.2)
1-5	654	635	97.0 (95.7-98.3)	50	7.64 (5.60-9.68)

Abbreviation: CI, confidence interval.

the segmental CTC report. This revealed 15 lesions in 13 participants. One was the 7-mm lesion noted and the other remaining lesions were 1 to 5 mm in size. In these 95 participants, 88% of the lesions reported by the CTC were false-positive. The CTC correctly identified 55 of 173 lesions sized at least 6 mm (sensitivity, 32.0%; 95% CI, 25.0%-38.9%), whereas conventional colonoscopy identified 170 lesions (sensitivity, 98.0%; 95% CI, 95.9%->99.9%) (TABLE 2). For lesions sized at least 10 mm, sensitivities were 52.0% (95% CI, 38.7%-65.3%) and 96.0% (95% CI, 90.8%->99.9%) for CTC and conventional colonoscopy, respectively.

Radiologists used 3-dimensional snapshots for trouble-shooting in 60% of the cases in which lesions were suspected. The rate of correct lesion identification was 28% when snapshots were used and 13% when they were not used.

Technical issues that might affect interpretation were analyzed. Several centers reported anecdotally that CTC interpretation was hindered by colon fluid but the data did not confirm this as a major issue. The CTC identified 14% of the lesions when preparation was rated optimal (small amount of fluid) and 10% when suboptimal (large amount of fluid or stool). There were no obvious differences with the type of colon distension (hand-pump or insufflator, air or carbon dioxide), presence or absence of diverticula, or whether the radiologist rated the report as confident.

Fly-through data were analyzed at a later date by the same radiology readers without referring back to their initial 2-dimensional review. The sensitivity and specificity for detecting participants with and without at least 1 lesion sized at least 6 mm were 45.0% (95% CI, 35.4%-54.6%) and 93.0% (95% CI, 90.8%-95.2%), respectively (TABLE 3). The sensitivity for detection of individual lesions was 15% for any size and 36.4% for those lesions sized at least 6 mm. Incorporating the fly-through data with the initial evaluation increased the sensitivity of CTC for the primary outcome (detection of participants with lesions ≥6 mm) by 17% to 56% but reduced specificity by 5%. For participants with lesions sized at least 10 mm, the fly-through data increased the sensitivity by 12% to 67%, and decreased the specificity by 1%.

The positive predictive values for conventional colonoscopy detection of lesions and participants were both 100% by definition because the conventional colonoscopy result was part of the criterion standard. The positive predictive values for CTC detection of lesions and participants and the negative predictive values for both procedures are shown in TABLE 4. The positive predictive value for CTC detection of participants with lesions sized at least 6 mm was 46.6% (95% CI, 42.9%-50.3%), and for those participants with lesions sized at least 10 mm was 50.0% (95% CI, 35.6%-64.4%). Negative predictive values for participants identified as not having a lesion sized at least 6 mm were 87.7% (95% CI, 84.9%-90.5%) for CTC and 99.8% (95% CI, 99.4%->99.9%) for conventional colonoscopy.

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Analysis of all cases across all sites by sequential accrual blocks of 10 participants showed no evidence for increased accuracy of CTC later in the study for participants with or without a lesion sized at least 6 mm ($P=.08$) or for lesions sized at least 10 mm ($P=.72$).

Of the 518 preference questionnaires that were returned to the clinical centers, 46% of the participants preferred CTC, 41% preferred conventional colonoscopy, and 13% had no preference. Participants were also asked to rate their experience compared with what they expected. For CTC, 62% stated that the procedure was better or much better than anticipated, 23% stated it was as anticipated, and 14% stated worse or much worse than anticipated. The respective data for conventional colonoscopy were 71%, 23%, and 6%. The respective ratings for the bowel preparation were 50%, 32%, and 18%.

Minor adverse events were experienced by 14 participants (2.3%). These included 1 episode of mild bleeding after polypectomy and 8 cases in which lesions of possible clinical relevance were observed outside of the colon on the CT scans.

COMMENT

The main result of this study was surprising and disappointing. The primary outcome measure, the sensitivity of CTC for the detection of participants with lesions sized at least 6 mm, was only 39% and was not much higher (55%) with a threshold of 10 mm. These data contrast remarkably with many other studies, almost all of which come from single-center studies in which the lead author was a radiologist. An obvious question is whether the radiologists in our study were sufficiently experienced. All were well trained and experienced in CT abdominal imaging. They had to have performed at least 10 CTC cases and have 5 recorded procedures reviewed centrally for quality, but not accuracy, before starting the study. Only 1 of the centers had substantial prior involvement with the technique. It contributed the most participants (n=184) and had the best results, with a primary outcome sensitivity of 82%. These data were very similar to previous data published from the same center.[15] The sensitivity for all other centers combined was only 24%, with no correlation between increasing experience and accuracy. Analysis of all the data in sequential blocks of 10 did not show any progressive improvement in accuracy as the number of cases increased (ie, no evidence of a "learning curve"). However, because there was no formal feedback to the participating radiologists

Table 3. Results of Fly-Through Interpretations

	Criterion Standard (No. of Participants)		Per Participant Sensitivity		Per Participant Specificity		Per Lesion Sensitivity		
Lesion Size, mm	True Positive	True Negative	No. of Participants With Detected Lesions	Sensitivity, % (95% CI)	No. of Participants Without Detected Lesions	Specificity, % (95% CI)	Total No. of Lesions	No. of Detected Lesions	Sensitivity, % (95% CI)
≥6	104	496	47	45.0 (35.4-54.6)	462	93.0 (90.8-95.2)	173	63	36.4 (29.2-43.6)
≥10	42	558	25	59.5 (44.7-74.3)	547	98.0 (96.8-99.2)	54	30	55.6 (42.3-68.9)
6-9	76	524	27	35.5 (24.7-46.3)	495	94.5 (92.5-96.5)	119	33	27.7 (19.7-35.7)
1-5	274	326	48	17.5 (13.1-21.9)	295	90.5 (87.3-93.7)	561	39	6.95 (4.85-9.05)

Abbreviation: CI, confidence interval.

Table 4. Positive and Negative Predictive Values for Computed Tomographic Colonography and Conventional Colonoscopy

	Computed Tomographic Colonography per Participant			Computed Tomographic Colonography per Lesion		
True Lesion Size, mm	Total No. of Participants With a Positive Test Result	No. of Participants With Lesions	Positive Predictive Value, % (95% CI)	Total No. of Lesions With a Positive Test Result	No. of Lesions	Positive Predictive Value, % (95% CI)
≥6	88	41	46.6 (42.9-50.3)	135	55	41.0 (32.7-49.3)
≥10	46	23	50.0 (35.6-64.4)	58	28	48.0 (35.1-60.9)
6-9	59	23	39.0 (26.6-51.4)	77	27	35.0 (24.3-45.7)
1-5	68	37	55.0 (43.2-66.8)	123	50	41.0 (32.3-49.7)
	Computed Tomographic Colonography per Participant			Initial Conventional Colonoscopy per Participant		
True Lesion Size, mm	Total No. of Participants With a Negative Test Result	No. of Participants Without Lesions	Negative Predictive Value, % (95% CI)	Total No. of Participants With a Negative Test Result	No. of Participants Without Lesions	Negative Predictive Value, % (95% CI)
≥6	512	449	87.7 (84.9-90.5)	497	496	99.8 (99.4->99.9)
≥10	554	535	96.5 (95.0-98.0)	558	558	100
6-9	541	488	90.2 (87.7-92.7)	525	524	99.8 (99.4->99.9)
1-5	532	295	55.5 (51.3-59.7)	335	326	97.3 (95.6-99.0)

Abbreviation: CI, confidence interval.

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during the trial, aspects of learning were missing. Only another study after intensive and specific training would clarify this issue. It is worrisome that a recent large study from the Mayo Clinic showed substantial variation in reporting among 3 radiologists, despite the fact that each had experience of more than 150 CTC examinations, with colonoscopy correlation.[18] Conversely, the Armed Services study had excellent results despite relatively little prior experience.[19]

The use of colonoscopy as the criterion standard in this study may be criticized, because colonoscopy cannot claim complete accuracy, even in the hands of experts.[22,23] Indeed, 2 large lesions were missed by colonoscopy in patients who had other identified lesions. However, this design, including segmental unblinding, has been used in other major studies and it is difficult to conceive of a realistic alternative.[15,19,20,24,25] The CTC reported numerous lesions that were not observed at the initial colonoscopy evaluation but 88% of these were judged to be false-positives when the endoscopist reexamined the suspect area.

The fly-through data were not included in the primary outcome because all centers could not guarantee to complete the readings within the 2-hour time frame before colonoscopy. Later analysis of the fly-through data did increase the sensitivity of CTC in our study and improved software now makes these elements easier and quicker to report.

Patient preference is an important issue, with discrepant results in the literature. Our participants did not indicate a strong participant preference for CTC over conventional colonoscopy but the use of sedation for most colonoscopies may be relevant. However, the preference question is complex and the answer may depend on how it is framed.[26,27] Participants might opt for CTC as seeming to be less invasive. However, the bowel preparation (now needed for both examinations) is the worst part. Many participants may opt to go directly to colonoscopy if they know that there is approximately a 20% chance that colonoscopy will be needed also for treatment, with a second bowel preparation.

The study recently reported from the Armed Services medical centers had remarkably different results.[19] In a screening population of 1233 adults, the CTC detected 93.8% of polyps sized more than 10 mm in diameter and 88.7% of participants with lesions sized more than 6 mm. The possible reasons for these results are being debated. The study differed from other studies in using 4-section and 8-section scanners, the 3-dimensional fly-through as the primary diagnostic tool, and intensive bowel preparation, including oral contrast and barium. It is not stated how the barium may have affected the accuracy of colonoscopy.

Even if the results of CTC continue to be good in the hands of experts, it has yet to be proven that this expertise can be taught and disseminated reliably into daily practice. There is an analogy with the barium enema examination. Published data mostly showed good accuracy but everyday experience was less satisfactory.[28]

Currently, CTC may have application in patients with obstructing tumors,[29,30] and in patients where colonoscopy is incomplete for other reasons.[31] The fact that the technique may detect extracolonic lesions can be observed as an advantage or a disadvantage.[32]

The CTC technology is evolving. Scanners are becoming more sophisticated and faster. Prepless CTC using electronically subtractable fecal markers is a tantalizing possibility.[33,34] The combination of electronic cleansing and faster 3-dimensional reconstruction appears promising.[35] Radiation exposure can be eliminated by using magnetic resonance scanning.[36] There is even the possibility of automating lesion recognition, which could greatly reduce the burden of reporting (now in excess of 1000 images per patient).[18,37,38]

Our results indicate that CTC using these techniques is not ready for routine use at this time, as many others have concluded.[4,7,39-41] There is an obvious need for continuing collaboration between radiologists and gastroenterologists in further evaluation of this exciting new technology. If and when results do justify widespread introduction, similar multidisciplinary collaboration will be needed to ensure its efficient application.

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Original article

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PillCam colon capsule endoscopy compared with colonoscopy for colorectal tumor diagnosis: a prospective pilot study

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Background and aims: Colonoscopy is regarded as the gold standard for colorectal cancer (CRC) screening. PillCam capsule endoscopy could be an alternative approach for screening large populations. We report a pilot evaluation in humans of the safety, feasibility, and performance of colon capsule endoscopy compared with colonoscopy.
Patients and methods: Patients included in this single-center comparative study had presented for screening colonoscopy or there was suspicion of polyps or CRC. The capsule was ingested in the morning. After excretion, colonoscopy was performed. Significant findings were defined either as polyps > 6 mm, or three or more polyps of any size. Colonoscopy and colon capsule endoscopy (CCE) review were performed by independent physicians.
Results: 41 patients (26 women), mean age 56 years (range 26 - 75) were included, and all had complete colonoscopies. Four patients were excluded due to technical problems and one could not swallow the capsule; thus, 36 patients were considered in the analysis. In six the capsule had not been expelled at 10 hours and was retrieved endoscopically. CCE identified 19 of the 25 patients (76 %) with positive findings and 10 of the 13 (77 %) with significant lesions detected by colonoscopy. CCE detected seven lesions not seen at colonoscopy and two tumors were detected by both examinations. Overall sensitivity of CCE to detect significant lesions was 77 %, specificity was 70 %, positive predictive value was 59 %, and negative predictive value was 84 %. No adverse events occurred.
Conclusion: CCE showed promising accuracy compared with colonoscopy. This new noninvasive technique deserves further evaluation as a potential CRC screening tool.

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Appendix SCHOOF02

N. Schoofs
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PillCam colon capsule endoscopy compared with colonoscopy for colorectal tumor diagnosis: a prospective pilot study

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Conclusion: CCE showed promising accuracy compared with colonoscopy. This new noninvasive technique deserves further evaluation as a potential CRC screening tool.

Introduction

Colorectal cancer (CRC) is the leading cause of cancer-related mortality in the western world [1]. There is a compelling evidence that early diagnosis and treatment of adenomas and cancer reduces the disease-specific mortality [2]. Colonoscopy is currently considered to be the gold standard procedure for CRC screening. Unfortunately, many patients are reluctant to undergo this examination because of its perceived inconvenience and the discomfort [3,4]. Although the cost-effectiveness of any screening program is still debated, awareness of CRC is growing and novel screening modalities such as computed tomographic colonography, or "virtual colonoscopy", and fecal DNA testing are emerging [5]. Self-propelling visualization devices are currently under investigation with the aim of reducing operator dependence and complications as well as improving acceptance [6]. The ideal screening method for CRC should be noninvasive, safe, well accepted by the target population, cost-effective, and with a high diagnostic accuracy.

Following the success of video capsule endoscopy for exploring the small bowel, colon capsule endoscopy could be an attractive approach to mass CRC screening.

Indeed, capsule endoscopy of the small bowel has already been established as the initial diagnostic investigation of choice in patients with obscure gastrointestinal bleeding [7,8] and in patients with suspected small-bowel lesions. At this stage, sufficient

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screening yield cannot be achieved in the colon by the standard small-bowel capsule because of the anatomical and physiological properties of the colon. The PillCam Colon capsule (Given Imaging, Yoqneam, Israel) was designed specially for colon exploration and differs from the standard small-bowel capsule in three ways. First, it has two imagers that enable the device to acquire video images from both ends. Secondly, it has the same diameter as the PillCam SB capsule but is approximately 6 mm longer; this increased capsule length is dictated by the need to achieve a specific weight-to-volume ratio which allows the capsule to progress into the colon within the desired time frame (up to approximately 10 hours from ingestion). Thirdly, the PillCam Colon capsule can work at a higher frame rate (4 frames per second) and is able to operate with a pre-programmed delay mode in order to save energy until it reaches the colon.

The aims of the present pilot study were to provide preliminary evaluation of the performance and accuracy parameters of the PillCam Colon capsule compared with traditional colonoscopy, and to evaluate the efficacy of colon preparation for colon capsule endoscopy (CCE).

Patients and methods

Patient population

Patients were considered for the study if they were scheduled to undergo colonoscopy, for CRC screening with or without a personal or family history of colorectal polyps or cancer (41 %; n = 17), or for unexplained abdominal pain or alarm symptoms (including rectal bleeding and altered bowel transit time) (59 %; n = 24). They were included between January 12 2006 and June 1 2006, all having been referred to the endoscopy department of our institution.

Exclusion criteria were as follows: age younger than 18 years; presence of dysphagia, congestive heart failure, renal insufficiency, intestinal obstruction, or pacemaker or other implanted electromedical device; pregnancy; abdominal surgery in the past 6 months; inability to understand patient information and/or give informed consent; presence of a life-threatening condition; and current participation in another clinical study.

The medical ethics committee of our institution approved the study and all patients provided written informed consent.

Colon preparation

Patients underwent a 24-hour colon preparation that consisted of a clear liquid diet after a light breakfast the day before CCE. Between 18.00 and 21.00 in the evening before capsule ingestion, patients received 3 l of an oral preparation of polyethylene glycol osmotic solution (Colopeg; Roche Laboratories, Gaillard, France), and another litre of this solution between 06.00 and 07.00 on the day of the examination. After 2 hours and 15 minutes following capsule ingestion patients drank a first boost dose of 45 ml of Sodium phosphate solution (Fleet Phospho Soda®, Wolf, Fleet, Lynchburg; Virginia, USA), only if the capsule was shown to have exited the stomach, as assessed with real time viewing system performed with Rapid Access Real Time Tablet PC (by Given Imaging Inc.) If the capsule was not excreted following the first boost dose of sodium phosphate a second boost dose of 30 ml sodium phosphate solution was administered at 14.00 (3 hours and 45 minutes after the first one), at 15.00 patients had a small low fiber snack and energy drink (e.g. Red Bull®). By 15.30, if the capsule was still not excreted, a suppository of bisacodyl (Dulcolax®, Boehringer Ingelheim, Scherer, Aprilia, Italy) was administered. The preparatory steps are summarized in Figure **1**.

Diagnostic procedures

Colon capsule endoscopy (CCE). The PillCam Colon capsule has two imagers that enable the device to acquire video images from both ends. It is 31 × 11 mm in size, and acquires pictures at a rate of 4 frames per second. The pre-programmed delay mode allows recording of images from the esophagus and the stomach for 5 minutes before the capsule switches into sleep mode for 2 hours to save energy. (A 2-hour delay was observed to be the most appropriate for the PillCam Colon capsule for it to reactivate in the terminal ileum in human volunteers.) The envelope of the PillCam Colon capsule is made of biocompatible materials, sealed with biocompatible adhesives, and produced according to similar procedures and guidelines as the standard PillCam SB and PillCam ESO capsules. Data were recorded in an external recording unit that receives the information transmitted by the ingested capsule. The portable recorder consists of an antenna array which is attached to the body, a receiver, and memory for data recording during the examination. Upon completion of the examination, the physician or the study nurse downloads the data from the recorder to the RAPID workstation for processing. The data transmission are transmitted via a high capacity digital link.

Interpretation of the data was always done by a different physician from the one who performed the colonoscopy. Reading of the colon capsule data was always done in two steps, first examining the images taken from one side of the device and then the images taken from the other side. The selected reading speed was around 7 – 12 frames per second.

The location of polyps within the colon was done with the help of the rapid localization feature. Polyps were classified with respect to the following: size (greater than or equal to 6 mm, or smaller than 6 mm); confidence rate (high or low); morphology (pedunculated, sessile, or flat); colon segment location (rectum, sigmoid, descending colon, transverse colon, ascending colon, or cecum); colour (pale, mucosal, reddish, or yellow); position (between folds, on fold, proximal side of fold, distal side of fold, or unknown); and surface (smooth, nodular, or ulcerated). All this information was entered into a case report form by the physician who read the CCE images.

All detected polyps were recorded as positive findings. CCE findings were considered significant if there was a polyp greater than 6 mm in size, and/or more than three polyps, and/or a suspected tumor. Other lesions such as angiomas, diverticuli, lipomas, proctitis, and hemorrhoids were also noted but not considered as significant findings.

Occasionally, real-time viewing was done during the CCE procedure to determine the location (stomach, small bowel, or colon) of the capsule, thus avoiding fluoroscopy during the procedure. A real-time display platform based on a laptop was connected to

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Time	Action
Day –1	
All day	Clear liquids only
18:00 – 21:00	3 Liters Colopeg® solution (1 cup every 10 – 15 minutes)
Exam Day[1]	
06:00 – 07:00	1 Liter Colopeg® (1 cup every 10 – 15 minutes)
07:00	Fast until Boost #1 (with the exception of Domperidone (Motilium®) and PillCam™ COLON ingestions)
07:45	20mg Domperidone (Motilium®) (with a cup of water)
08:00	PillCam™ COLON ingestion (with a cup of water)
10:00	Boost #1[2]: 45ml oral sodium phosphate (Fleet Phospho-Soda®) + 1 Liter water
14:00	Boost #2 : 30ml oral sodium phosphate (Fleet Phospho-Soda®) + 1 Liter water
15:00	Optional light snack (low fiber) Fast until conventional colonoscopy procedure
16:30	10mg Bisacodyl (Dulcolax®) rectal suppository
19:00	Conventional colonoscopy performed

1) Colon preparation and procedure on day of PillCam™ COLON examination was performed on-site. When PillCam™ COLON was excreted early, the regimen was discontinued and patient was prepared for conventional colonoscopy.

2) The timing of Boost #1 was delayed if PillCam™ COLON was delayed in the stomach for longer than 2 hours post ingestion as detected with real-time viewing performed with Rapid Access Real Time Tablet PC (by Given Imaging Inc.).
– If PillCam™ COLON had moved out of the stomach, the colon regimen was continued as describe above.
– If PillCam™ COLON was delayed in the stomach, Boost #1 was administered only when PillCam™ COLON was found by real-time viewing to have moved out of the stomach and the regimen related to Boost #2 and Bisacodyl suppository changed forward as follows:

If Boost #1 was administered during the time period indicated below	Then Boost #2 was administered at the time indicated below	And Bisacodyl suppository was administered at the time indicated below
10:00 – 11:00	14:00	16:30
11:00 – 12:00	Time of 1st boost + 3 hours	16:30
12:00 – 13:00	Time of 1st boost + 3 hours	17:00
13:00 – 14:00	Time of 1st boost + 3 hours	No suppository
14:00 – 16:00	No Boost #2	No suppository
No boosts and suppository if PillCam™ COLON stayed in stomach after 16:00		

Figure **1** PillCam® COLON preparation and procedure regimen.

the data recorder that was carried by the patient. In this way, the video images that were transmitted by the device were displayed in real time on the screen.

Colonoscopy. Patients underwent colonoscopy with a standard colonoscope (CF-160; Olympus, Tokyo, Japan) at the endoscopy department in the one-day clinic at our institution. The endoscopic procedure was done after expulsion of the capsule or when the battery was exhausted. All colonoscopies were performed by an experienced endoscopist, with the patient under general anesthesia with propofol (Diprivan; Astra Zeneca, Sweden) and without endotracheal intubation. All examinations were recorded on videotape and still pictures were taken and recorded on the Endobase system (Olympus, Tokyo, Japan).

During colonoscopy the endoscopist classified polyps, if present, with respect to size; distance from the anal margin; morphology (pedunculated, sessile, flat); location (rectum, sigmoid, descending colon, transverse, ascending colon, or cecum); colour (pale, mucosal, reddish, or yellow); position (between folds, on fold, proximal side of fold, distal side of fold, or unknown); and surface (smooth, nodular, or ulcerated). All this information was entered into a case report form by the physician who performed the examination.

Further data. At the end of the colonoscopy patients were questioned about comfort and possible inconvenience regarding each technique. Adverse events for both procedures were documented. In the case of positive CCE with negative colonoscopy, the study protocol did not envisage a second colonoscopy.

Data analysis

The CCE and colonoscopy examinations were carried out by two independent physicians, each of whom was blinded to the results of the other procedure. The potential role of a noninvasive screening method is to select patients with polyps who might benefit from therapeutic endoscopy. Although some experts recommend that only polyps that are 10 mm or more in size should be removed, we defined as a "significant finding" the presence of either a polyp greater than 6 mm or of three or more lesions of any size, or a tumor. In addition, all polyps of any size were noted as positive findings.

For all the defined lesions we calculated the "per patient" sensitivity, the specificity, and the positive predictive value (PPV) and negative predictive value (NPV) of CCE in comparison with colonoscopy.

Other lesions such as angiomas, diverticula, lipomas, proctitis and hemorrhoids were also noted but not considered in the anal-

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ysis. The colon cleansing level was rated for the CCE and for colonoscopy, using a scale of 1 to 4 (poor, fair, good, and excellent) for each section of the colon, according to the Minimal Standard Terminology of digestive endoscopy [9]. An interobserver agreement study was done by two independent physicians.

Although it was not regarded as an initial aim of this study, the description of the lower esophagus and the Z line was done for all patients.

Statistical analysis

Descriptive statistics were expressed as the median and range values for continuous variables. Percentage values are rounded off to the nearest whole number. We considered the colonoscopy to be the gold standard against which CCE was compared. The diagnostic yield of CCE was assessed, and sensitivity, specificity, positive and negative predictive values (PPV and NPV) per patient were calculated. Statistical analyses were done with SPSS software, version 11.0 (SPSS Inc., Chicago, Illinois, USA) and CIA (Confidence Interval Analysis) software, version 2.0.0 (Trevor N. Bryant 2000, Southampton, UK).

Interobserver agreement analysis was carried out by two independent reviewers for each detected lesion. We assessed the presence and the number of significant findings. Reviewers were considered to agree on a finding according to the size, location, and timing of reviewing of the recordings. Kappa statistics with 95 % confidence intervals were calculated.

Results

Baseline characteristics

Between January 12 2006 and June 1 2006, 41 patients (26 women; mean age 56 years, range 26 – 75) agreed to participate in the study and were referred to the endoscopy unit for colonoscopy preceded by CCE. Three patients out of the first five in the series were excluded from the data analysis due to technical problems: re-activation of the capsule occurred late or not at all, so less than 30 % of the colon was visualized. One patient could not swallow the capsule because of excessive anxiety; this patient underwent only colonoscopy. Finally, another patient underwent both examinations, but reading of the CCE images was hindered by technical problems in the data transmission from the recorder to the workstation. Therefore, 36 patients were finally included in the study.

CCE findings

No adverse events were documented. In six patients (16 %) the capsule was not expelled at the end of the recording time (10 hours); at that time, the capsule was located in the cecum in one patient, the transverse colon in one patient, the sigmoid in three, and the rectum in one patient. In these patients the capsule was retrieved using a snare during colonoscopy.

The mean time taken to read the CCE images was 62 minutes (range 45 – 90 minutes), with a speed range of 7 – 12 frames per second. All the PillCam Colon capsules passed the stomach, and 35 of them (97 %) re-activated in time, before reaching the ileocecal valve. The overall preparation was evaluated as excellent in 30 % of cases, as good in 58 %, as fair in 6 %, and as poor in 3 %.

Table **1** Findings of PillCam Colon capsule endoscopy and colonoscopy in the study population (n = 36)

	Positive colonoscopy, n	*Negative colonoscopy, n*
Any findings		
CCE positive	19	4
CCE negative	6	7
Polyps > 6 mm		
CCE positive	6	7
CCE negative	4	19
≥ 3polyps		
CCE positive	5	9
CCE negative	3	19
Polyp > 6 mm or ≥ 3 polyps		
CCE positive	10	7
CCE negative	3	16

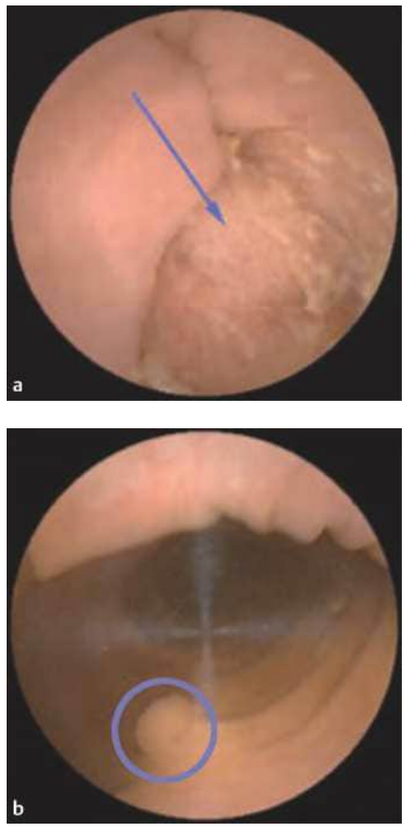
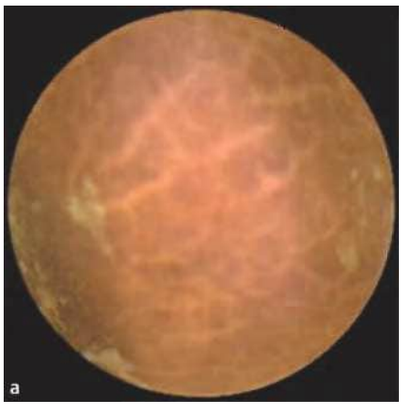


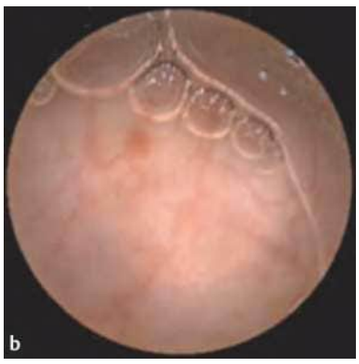
Figure **2** PillCam Colon capsule endoscopy images: **a** a tumor; and **b** a polyp.

CCE findings were positive in 23 patients and negative in 13 patients (details are provided in Table **1**). Apart from polyps (Figure **2**), several types of lesions were observed and documented, such as angiomas (n = 1), melanosis coli (n = 3), diverticuli (n = 25), proctitis (n = 1) and the India-ink injection site from a previous polypectomy (n = 1), but these were not considered when reporting the results of this study (Figure **3**).

Interobserver agreement with regard to significant lesions was 80.5 %.

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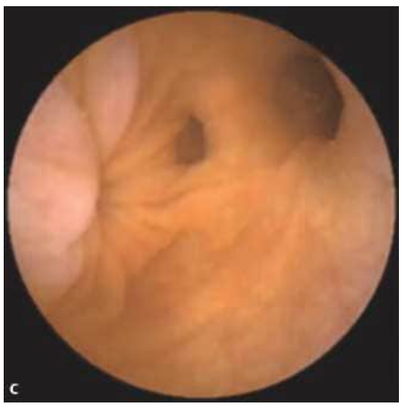


Figure **3** Colon capsule endoscopy (CCE) images: **a** melanosis coli; **b** angioma; and **c** diverticuli.



Figure **4** CCE image of the Z-line.

Comparison of PCCE and colonoscopy

CCE was negative in six out of 25 patients with positive colonoscopic findings, but was positive in four patients with negative colonoscopy.

Regarding the presence of a polyp greater than 6 mm in size, CCE was negative in four out of 10 patients with positive findings and was positive in seven out of 26 patients with negative findings at colonoscopy. A second reading of the recordings of the false-negative CCEs allowed identification of a bigger than 6 mm polyp in only one of the four patients; the size of this polyp was initially considered to be less than 6 mm.

Concerning detection of at least three polyps, CCE was negative in three out of eight patients with positive colonoscopy findings, and positive in nine out of 28 patients with negative colonoscopy. The patient sensitivity, specificity, and the positive and negative predictive values for the CCE regarding positive findings and the significant finding are detailed in Tables **2–4**. Interestingly, for polyps larger than 6 mm in size, the positive predictive value and the negative predictive value were 46% and 83%, respectively.

Esophageal data

The lower esophagus as well as the Z-line were well visualized in 60% of the 36 patients (Figure **4**).

Colonoscopy

Complete colonoscopy, including examination of the cecum, was achieved in all cases. All procedures were successfully performed with all the patients under general anesthesia without intubation, except for one who had severe chronic obstructive lung disease. There were no adverse events. Each colonoscopy was performed the same day as the CCE, after excretion of the capsule or when recording of images had stopped.

Colonoscopy showed positive findings in 25 patients, and was negative in 11 patients (details are provided in Table **1**).

A subjective assessment questionnaire was given to each patient after colonoscopy and complete resposes were obtained from 33 patients. Three patients (9%) described colonoscopy under general anesthesia as more comfortable than CCE.

Discussion

The main message to be taken from this study is that CCE with the PillCam Colon capsule is feasible, and can provide good quality images of the entire colon and can detect polyps and tumors in the majority of cases. This was achieved by both technical development of the capsule itself and adaptations of the bowel preparation. The presence of two imagers undoubtedly enhances the capabilities for detection, since some of the polyps we observed were visible only on one side of the recorder. The pre-programmed delay mode was a partial solution to the problem of battery life duration, and it appeared that the 2-hour inactive period, calculated on the basis of data collected in previous studies with healthy participants, was adequate for patients since all but one colon capsule re-activated before reaching the cecum. Complete visualization of the colon was not achieved before the

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Table **2** Diagnostic discrimination, with 95% confidence interval (95% CI), of PillCam Colon capsule endoscopy, for detecting three polyps or more in the study population (n = 36)

	%	*95% CI, %*
Sensitivity	63	29 – 96
Specificity	68	51 – 85
Positive predictive value	36	11 – 61
Negative predictive value	86	72 – 101

Table **3** Diagnostic discrimination of colon capsule endoscopy (CCE), for any findings* in the study population (n = 36)

	%	*95% CI, %*
Sensitivity	76	59 – 93
Specificity	64	35 – 92
Positive predictive value	83	67 – 98
Negative predictive value	54	27 – 81

* Any findings, i. e. all kinds of polyps.

Table **4** Diagnostic discrimination of CCE, for polyps larger than 6 mm in size in the study population

	%	*95% CI, %*
Sensitivity	60	30 – 90
Specificity	73	56 – 90
Positive predictive value	46	19 – 73
Negative predictive value	83	67 – 98

end of battery life in 16% of the patients, however, underlining the need for further improvement.

The colonic preparation was adapted not only to clean the colon but also to facilitate the progression of the capsule, with the administration of one or two boosts of sodium phosphate. Excellent or good preparation for CCE was achieved in 90% of cases. All the patients tolerated the preparation without any significant complaint. The present study was notable in that all the patients underwent the same preparation for both examinations, which were performed on the same day. This was an important point for assuring uniformity and comparability of the two techniques. Some additional fine tuning of the preparation might help to avoid the presence of opaque liquid that compromises complete visualization during CCE.

Standard colonoscopy was regarded as the gold standard in our study. Despite this being a pilot study, and given our lack of previous experience in reading colon capsule images, significant lesions (an indication for therapeutic colonoscopy) were detected with high levels of sensitivity and specificity (77% and 70%). The negative predictive value (84%) is the highest and this is potentially important since one of the aims of such an examination would be to obviate the need for additional examination by standard colonoscopy. These values have to be put alongside those of colonoscopy itself, when performed two times. A recent review of six studies reporting two same-day colonoscopies reported miss rates of 13% and 26% for adenomas of 5 – 10 mm and 1 – 5 mm, respectively [10]. Also CCE identified lesions which were not seen at colonoscopy (in four patients who had no findings at all at colonoscopy). The PillCam Colon capsule takes images from both its ends, perhaps improving visualization of lesions located "behind the folds", which are easily missed during colonoscopy. Even polyps larger than 6 mm in size were detected in seven patients in whom colonoscopy had failed to detect them. These discrepancies could also be due to a difference in size assessment at colonoscopy and CCE, with a possible overestimation associated with the latter. An accurate evaluation of missed lesions, either by colonoscopy or CCE, would imply the need to repeat colonoscopy (after analysis of the CCE) in every patient having any findings seen only by CCE.

The interobserver agreement for PCCE was 80%, suggesting that there is still room for improvement and that a learning curve will be mandatory. The current levels of sensitivity and specificity are encouraging when compared with those of virtual computed tomography (CT) colonoscopy (in two major series the reported negative predictive values were 98% and 91% [11,12]), or those of colonoscopy itself (a tandem colonoscopy study by Rex et al. showed that the first colonoscopy has a negative predictive value of only 84% for detecting adenomas of any size) [13]. Two multicentric studies are planned in order to further evaluate the accuracy of CCE compared with colonoscopy for screening CRC.

Compared with other techniques of virtual colonoscopy, such as CT or magnetic resonance imaging (MRI), CCE is different in that size is not a limitation for detection since very small lesions are clearly visible. After having carried out these examinations we realized that among all the screening techniques currently available, CCE is the only one that could be performed by patients themselves without the intervention of a physician, provided that clear explanation could be offered. This could therefore be proposed as a test to be carried out at home, and improve the acceptance for mass screening.

Finally, although we did not ask the patients to swallow the capsule while in the decubitus position as is done in PillCam esophageal studies, the Z-line was clearly visualized in 60% of cases. The investigation of this finding in further studies is obviously justified, since the population who may benefit from CRC screening may coincide to some extent with the population for whom detection of Barrett's esophagus might be useful [14].

In conclusion, this pilot study evaluating CCE done on the same day as colonoscopy shows that it is feasible, allows the examination of the entire colon in the majority of cases, and provides encouraging sensitivity and negative predictive values for detection of significant lesions. Further studies are needed to confirm this accuracy, the technique being potentially also useful for detection of Barrett's esophagus.

Acknowledgments

This study was supported by Given Imaging.

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In brief

Colon capsule pilot trial from a single center on 36 cases (5 excluded due to technical reasons) with 77% sensitivity and 70% specificity when compared to colonoscopy performed the same day with the same colon preparation. Further progress can be awaited.

The authors thank Erik Francois for critical review of the manuscript, Marianna Arvanitaki for helpful discussions, Philippe Golstein for recruiting patients and performing endoscopies, Nele Dustin and Marianne Defevrimont for the general anesthesia of the patients during colonoscopy, and Sabine Luyckx, Valerie Wambacq, Graziella Viste, and Martine Mahieu for their nursing of the patients during endoscopy and recovery.

Competing interests: The study was supported by Given Imaging.

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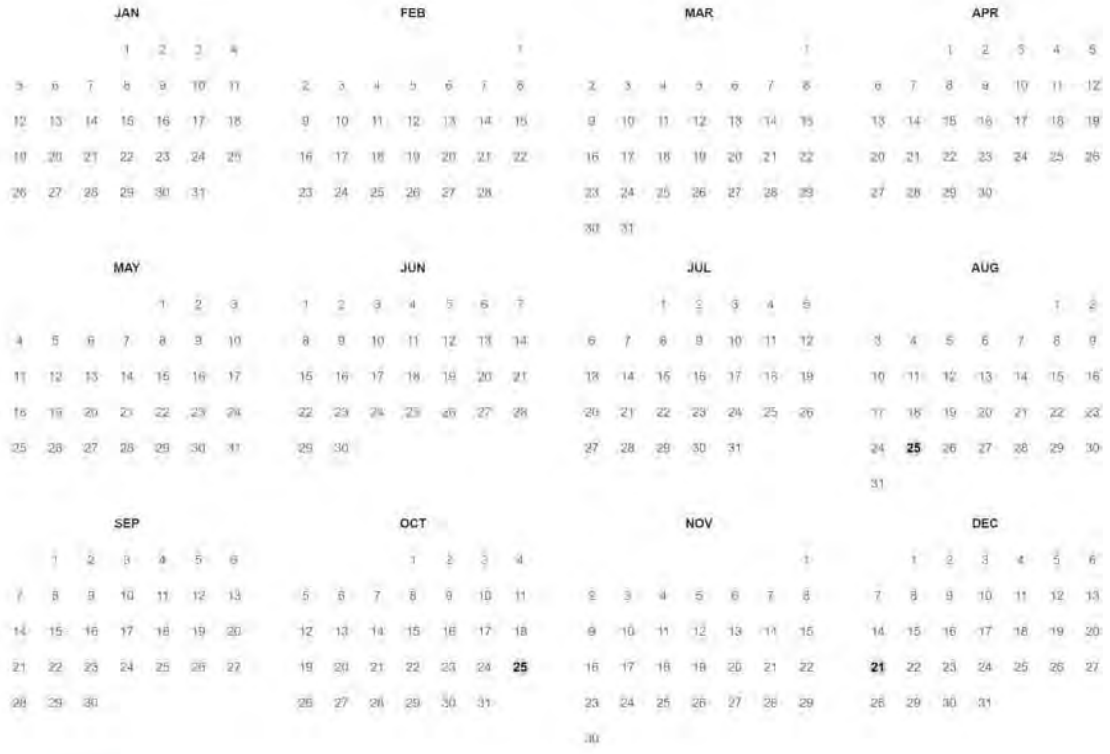
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Latest News

FDA APPROVES EXACT SCIENCES' COLOGUARD®; FIRST AND ONLY STOOL DNA NONINVASIVE COLORECTAL CANCER SCREENING TEST

August 12, 2014 / by **Exact Sciences**

MADISON, WI – Exact Sciences Corp. (NASDAQ: EXAS) announced today that the U.S. Food and Drug Administration (FDA) has approved Cologuard, the company's noninvasive, stool DNA colorectal cancer screening test. Cologuard is the first noninvasive screening test for colorectal cancer that analyzes both stool DNA and blood biomarkers and has been proven to find 92 percent of cancers and 69 percent of the most advanced precancerous polyps in average risk patients. Cologuard, which is available through healthcare providers, offers people 50 and older at average risk for colorectal cancer an easy-to-use screening test they can do in the privacy of their own home.

Upon approval, Exact Sciences also received a proposed coverage memorandum from the Centers for Medicare and Medicaid Services (CMS). Cologuard is the first product to take part in the joint FDA and CMS parallel review pilot program in which both agencies simultaneously review medical devices to help reduce the time between FDA approval and Medicare coverage. A final National Coverage Determination is expected to be posted in October/November of this year after a public comment period.

Colorectal cancer is considered the most preventable, yet least prevented cancer due to the lack of patient compliance with screening. An estimated 23 million Americans between 50 and 75 are not getting screened as recommended and as a result, colorectal cancer remains the second-leading cancer killer in the U.S. For those whose cancer is detected at an earlier stage, the five-year survival rate can be greater than 90 percent.

"Colorectal cancer is highly preventable and following the recommended screening guidelines can lead to life-saving early detection," said Eric Hargis, CEO, Colon Cancer Alliance. "In more than 60 percent of all cases, colorectal cancer is not detected until its late stages, making treatment more challenging. New, patient-friendly screening options are desperately needed to prevent colorectal cancer or help identify it early, when it is most treatable. Given that more than half of colorectal cancer-related deaths could be avoided with regular screenings, having Cologuard as another option for people who have resisted getting a colonoscopy could result in many lives being saved and screening compliance rates to increase."

Cologuard is designed to detect biomarkers from DNA in cancer that is shed from the colon as part of the digestive process and blood released in the stool. After the physician orders Cologuard, the kit is mailed directly to the patient's home. The patient then collects a stool sample in the Cologuard Collection Kit and sends the kit back to the Exact Sciences lab for testing through a pre-paid mailer.

At the lab, the stool sample is analyzed in an automated system to yield a single test result—positive or negative for the presence of precancerous polyps or cancer. Results from the Cologuard test are turned around in as little as two weeks, and patients learn their results directly from their prescribing physician. Unlike many other screening options, Cologuard does not require medication or dietary restrictions, or bowel preparation prior to taking the test.

"The robustly conducted research as part of this FDA approval process has proven that this noninvasive test is highly sensitive in detecting both early stage colorectal cancer and the most advanced

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precancerous polyps most likely to develop into cancer," said David Ahlquist, M.D., a Mayo Clinic gastroenterologist and co-inventor of the test. "The test is designed for high accuracy, ease of patient use, and wide accessibility. We hope that it will make a difference and save many lives."

"The FDA approval of Cologuard represents a major achievement in Exact Sciences' mission to make a noninvasive, patient-friendly screening test for colorectal cancer available," said Kevin Conroy, President, CEO and Chairman of Exact Sciences. "Cologuard addresses a critical need for a more convenient screening option for patients to aid in prevention and early detection. Exact Sciences is committed to making Cologuard available and accessible to patients and looks forward to advancing cancer detection in other gastrointestinal cancers. On behalf of the Exact Sciences team, I would like to thank the FDA and CMS for allowing us to go through the parallel review process."

Results from the company's DeeP–C Study, prospective, 90–site, 10,000–patient pivotal study—one of the most extensive colorectal cancer screening studies ever conducted in the U.S.—were published in April 2014 in the *New England Journal of Medicine's*, "Multi-target Stool DNA Testing for Colorectal-Cancer Screening".

Cologuard is available to patients through their healthcare providers in the U.S. for $599. Exact Sciences has plans to make Cologuard available in select countries in Europe pending CE Mark. For more information, visit www.CologuardTest.com or call 1-844-870-8870. More information on colon cancer and the importance of screening and early detection athttp://www.beseengetscreened.com/. Visit www.exactsciences.com to to sign up for the company's eNewsletter.

Dr. David Ahlquist, professor of medicine at Mayo Clinic, is the inventor of the technology that has been licensed to Exact Sciences from Mayo Clinic. Under that licensing agreement, Mayo Clinic and Dr. Ahlquist share in equity and royalties. Revenue Mayo Clinic receives is used to support Mayo's not–for–profit mission in patient care, education and research.

About Exact Sciences Corp.

Exact Sciences Corp. (NASDAQ: EXAS) is a molecular diagnostics company focused on the early detection and prevention of colorectal cancer. The company has exclusive intellectual property protecting its noninvasive, molecular screening technology for the detection of colorectal cancer. Stool DNA technology is included in the colorectal cancer screening guidelines of the American Cancer Society and the U.S. Multi–Society Task Force on Colorectal Cancer. For more information, please visit the company's website at www.exactsciences.com, follow us on Twitter @ExactSciences or find us on Facebook.

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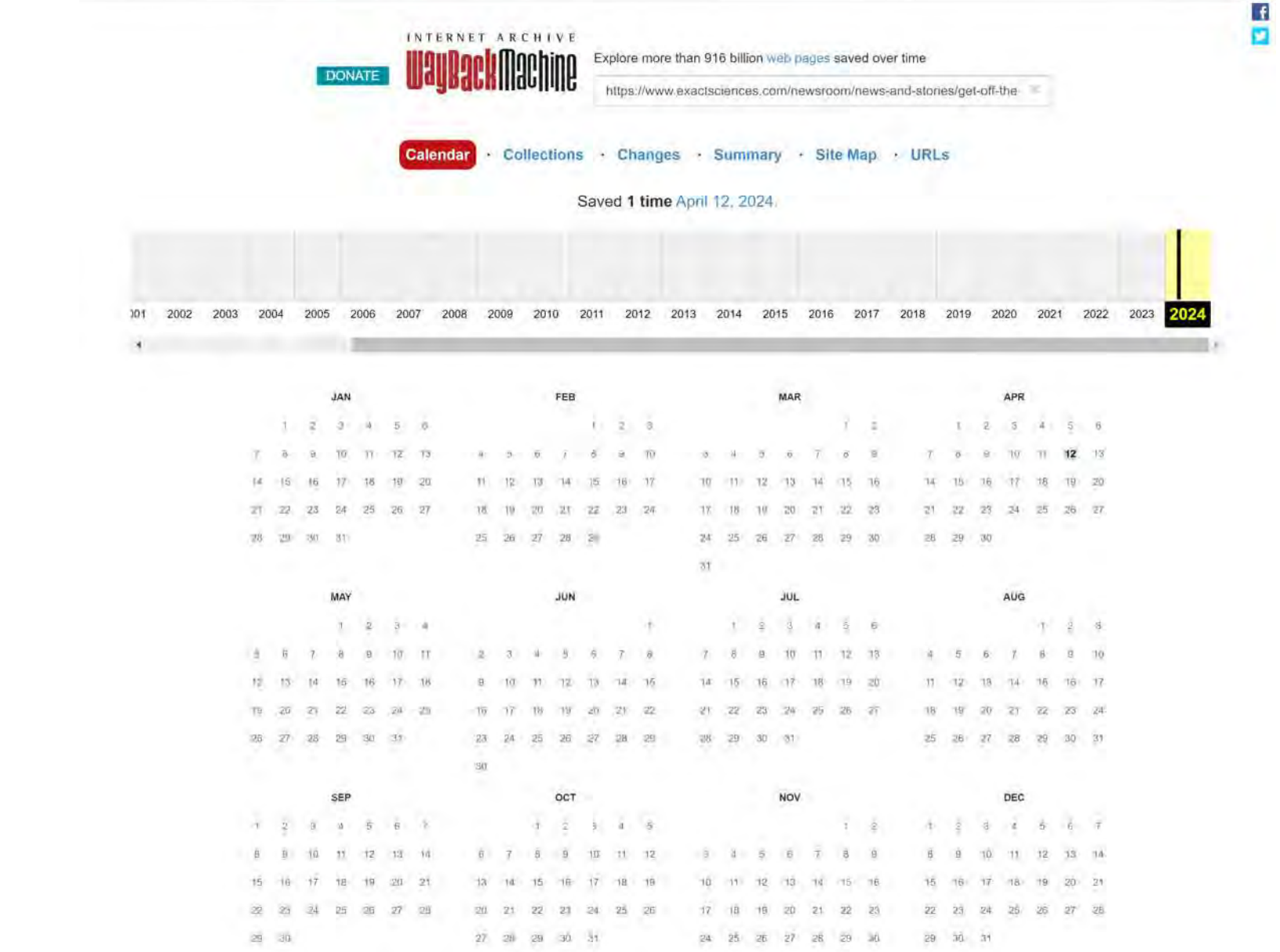
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March 07, 2024

GET OFF THE BENCH: HOOPS-THEMED CAMPAIGN URGES COLORECTAL CANCER SCREENING

Basketball great Jamal Mashburn joins Exact Sciences and The Blue Hat Foundation to 'Box Out Colon Cancer.'



Exact Sciences

Shortly after basketball star Jamal Mashburn entered the NBA in the 1990s, he got some tough news.

His mother, Helen, had been diagnosed with colon cancer.

"My mom was my best friend and my biggest cheerleader," Mashburn says. "She taught me to dream on and off the court. Every game, I always thought about her, and every day now, I still try to make her proud."

To honor his mother, Mashburn is challenging people 45 and older to get screened for colorectal cancer (CRC). His teammates in this effort: The Blue Hat Foundation, a nonprofit dedicated to raising CRC awareness and access in minority and medically underserved communities, and Exact Sciences, the maker of the CRC screening test Cologuard®.

March is Colorectal Cancer Awareness Month. It's also a big month for hoops, with all eyes on the annual NCAA college basketball tournament — longtime fans will remember Mashburn leading his team deep into the bracket in 1993.

Basketball fans also know that the best defense is a good offense. CRC screening advocates know that as well. CRC is the nation's no. 2 cancer-related killer,[1] and it's on the rise at alarming rates among younger people.[2] It's also treatable in about 90% of those diagnosed when caught in the early stages.[3,*]

BOX OUT COLON CANCER

The Box Out Colon Cancer campaign will mark college basketball's biggest moment while raising CRC awareness. In basketball, "boxing out" is a defensive fundamental that involves out-hustling and out-positioning your opponent to keep control of the ball — and the game. In CRC prevention and detection, it means getting screened when you're 45 or older, as recommended by the American Cancer Society.[4]

Four out of five adults ages 45-49 remain unscreened for CRC.[5]

While everyone age 45 and older could benefit from CRC screenings, the need is particularly critical for the African American population. That group is about 20% more likely to develop — and about 40% more likely to die — from CRC than most other groups.[6]

The Blue Hat Foundation knows this. The nonprofit combines sports enthusiasm and vital health education to promote CRC screening in at-risk communities, especially young adults and African American men.

"We are honored to join Exact Sciences in putting a full-court press on breaking colon cancer screening stigmas, particularly in the Black community," says Candace Henley, founder of The Blue Hat Foundation. "Together, we can Box Out Colon Cancer, one screening at a time."

Cologuard is the first FDA-approved, noninvasive, at-home stool-based CRC screening test for average-risk individuals 45 years or older. In the decade since its launch, people have used Cologuard more than 14 million times. Using data from the test's pivotal clinical study, Exact Sciences estimates that Cologuard may have detected more than half a million instances of precancerous polyps or early-stage CRC.

"At Exact Sciences, we work hard to drive awareness of the importance of timely colorectal cancer screening and to provide an accurate and easy-to-use option for people to screen from home," says Paul Limburg, Exact Sciences chief medical officer, Screening. "We are thrilled Jamal Mashburn and The Blue Hat Foundation share the same passion for getting people screened, and our hope is to inspire and motivate people ages 45 and up to take action and get screened."

As Mashburn helps to spread screening awareness on a large scale, his mother is always on his mind.

"I wish we knew how crucial routine screening is before she was diagnosed," he says. "Being more preventive and checking into your health has the potential to save your life."

Learn more at BoxOutColonCancer.com.

NOTES AND REFERENCES

* Based on five-year survival.

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DIVE DEEPER INTO COLORECTAL CANCER



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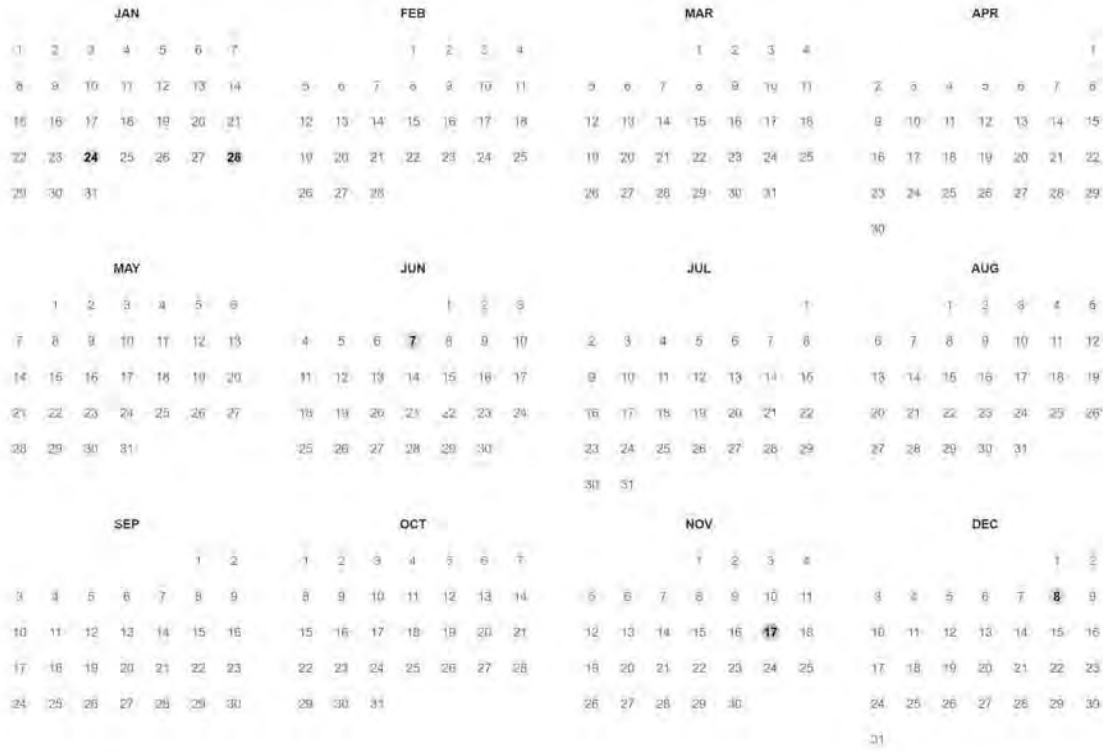
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PRESS RELEASE

Geneoscopy Submits Premarket Approval Application to FDA for its Noninvasive Colorectal Cancer RNA Biomarker Screening Test

By: Geneoscopy | January 24, 2023

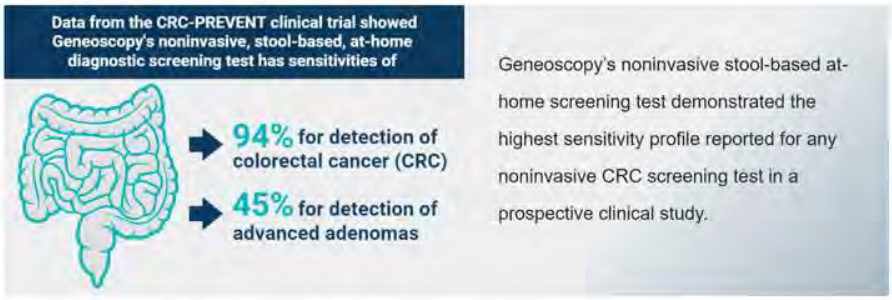
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FDA's Decision Forthcoming for Innovative Test with Agency's Breakthrough Device Designation

ST. LOUIS, Jan. 24, 2023 / — Geneoscopy, Inc., a life sciences company focused on the development of diagnostic tests for gastrointestinal health, announced today it submitted a Premarket Approval (PMA) application to the U.S. Food and Drug Administration (FDA) for its noninvasive, stool-based, at-home screening test to detect colorectal cancer (CRC) and advanced adenomas (AA) in average-risk individuals. The FDA designated the test as a Breakthrough Device in January 2021.

"Over 50 million Americans between the ages of 45 and 85 are eligible to be screened for CRC.[1,2] Unfortunately, despite CRC being the second leading cause of cancer death in the U.S., millions of eligible Americans do not get screened – many due to a lack of knowledge of the importance of screening, lack of access to screening and concerns about the invasive nature of options like colonoscopy," said Dr. Erica Barnell, Chief Science Officer and Geneoscopy's co-founder. "We are committed to closing this gap for patients who require screening and look forward to working with the FDA to bring a convenient and reliable screening option to patients that may allow for earlier detection and treatment – and potentially save lives."

The PMA submission is based on the favorable results from the pivotal CRC-PREVENT trial, in which Geneoscopy's test demonstrated 94% sensitivity for CRC and 45% sensitivity for advanced adenomas, representing the highest sensitivity profile reported to date for any noninvasive CRC screening test in a prospective clinical study.



Additionally, in the 45-49 age population, Geneoscopy's test demonstrated 100% sensitivity for cancer and 44% sensitivity for advanced adenomas, at an 89% specificity. CRC-PREVENT is the first prospective study of a stool-based test to report CRC sensitivity in patients ages 45-49, an age group most recently added to the recommended screening population by the United States Preventive Services Task Force and the American Cancer Society. The robust sensitivity profile for CRC and advanced adenomas will offer significant value to this patient population.

Related Articles

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Geneoscopy Receives Accreditation from the College of American Pathologists (CAP) for its St. Louis Clinical Laboratory
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Geneoscopy announces rebranding
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Geneoscopy Completes Pivotal Colorectal Cancer Trial Enrollment with Diverse Participant Population
September 27, 2022

Geneoscopy to Join Fight CRC at the White House to Address Colorectal Cancer Screening Needs
July 19, 2022

"The completion of our PMA submission is a major milestone – Geneoscopy's first regulatory approval application," said Andrew Barnell, Chief Executive Officer and Geneoscopy's co-founder. "This product and the years of effort from our team that have brought us here exemplify the dedication to our mission to empower patients and providers to transform gastrointestinal health through innovative diagnostics. The impact this test can have on patient health is beyond exciting, as is the validation of our stool RNA platform. We believe this platform will yield additional tests, including increasingly more precise CRC screening and high-value diagnostic testing for other gastrointestinal indications."

About CRC-PREVENT

CRC-PREVENT was a Phase 3 prospective, single-arm study designed to evaluate the efficacy of Geneoscopy's noninvasive, stool-based, at-home screening test to detect colorectal cancer and advanced adenomas in average-risk individuals. Using a collection kit, participants submitted self-collected stool samples via express delivery and underwent an optical colonoscopy examination. All significant lesions discovered during the colonoscopy were biopsied or removed and sent for histopathology. A comparative analysis was conducted to determine sensitivities and specificities for colorectal cancer, advanced adenomas, non-advanced adenomas, hyperplastic polyps, and colonoscopies with no findings.

About Colorectal Cancer & Screening

Responsible for over 50,000 deaths annually, colorectal cancer (CRC) is the second leading cause of cancer death in the United States.CRC usually begins as a growth (or polyp) that may or may not develop into cancer over time. Early detection and treatment are crucial to improve survival; however, many newly diagnosed patients suffer from advanced disease. Colonoscopy remains the gold standard for CRC screening in the U.S. Yet this method is frequently met with patient aversion due to its required bowel preparation, sedation, and potential time away from work. Currently available noninvasive screening methods demonstrate lower sensitivity to detect early-stage CRC and high-risk precancerous lesions, including advanced adenomas, which are estimated to be a precursor in 95 percent of CRC cases.[3]

About Geneoscopy Inc.

Geneoscopy Inc. is a life sciences company focused on developing diagnostic tests for gastrointestinal health. Leveraging its proprietary, patented stool-derived eukaryotic RNA (seRNA) biomarker platform, Geneoscopy's mission is to empower patients and providers to transform gastrointestinal health through innovative diagnostics. Beyond colorectal cancer screening, Geneoscopy is developing tests for diagnosis, treatment selection, and therapy monitoring in other disease areas in partnership with leading universities and biopharmaceutical companies. For more information, visit www.geneoscopy.com and follow the company on LinkedIn.

Geneoscopy Inc. Forward-Looking Statements

The information in this release includes information about Geneoscopy's future plans concerning its noninvasive molecular test that can detect colorectal cancer and precancerous adenomas, which constitute forward-looking statements. These forward-looking statements are based on the Company's reasonable estimates of future results or trends. Because forward-looking statements relate to the future, they are subject to inherent uncertainties, risks and changes in circumstances that are difficult to predict, many of which are outside the Company's control. Geneoscopy's actual results and financial condition may differ materially from those indicated in the forward-looking statements. Although the Company believes that its business plans and objectives reflected in or suggested by these forward-looking statements are reasonable, such plans or objectives may not be achieved, and the actual results may differ substantially from the projected results.

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media@geneoscopy.com

References

1. *Colorectal Cancer Screening in U.S. Seniors ages 76-84 Years*. (2016, August 1). NCBI. Retrieved January 19, 2023, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4491009/
2. *Estimating the Screening-Eligible Population Size, Ages 45-74, at Average Risk to Develop Colorectal Cancer in the United States*. (n.d.). PubMed. Retrieved January 19, 2023, from https://pubmed.ncbi.nlm.nih.gov/32029430/
3. Lin JS, Piper MA, Perdue LA, et al. *Screening for Colorectal Cancer: A Systematic Review for the U.S. Preventive Services Task Force* [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2016 Jun. (Evidence Syntheses, No. 135.) 1, Introduction. Available from: https://www.ncbi.nlm.nih.gov/books/NBK373586/

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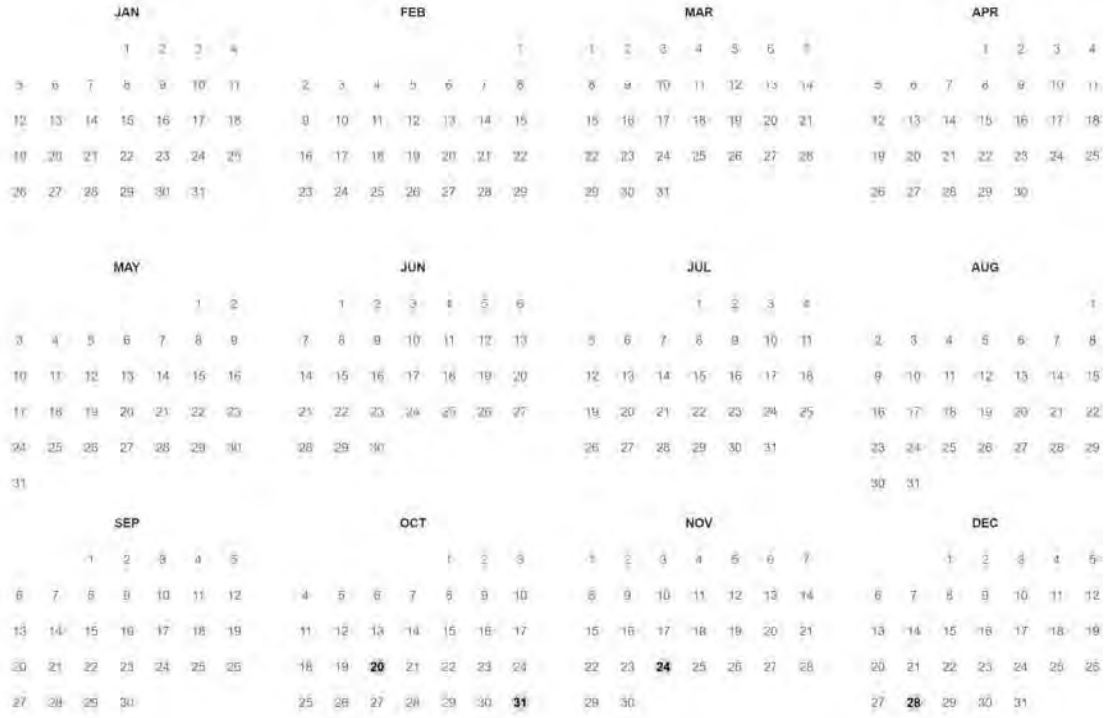
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Increase the proportion of adults who get screened for colorectal cancer — C-07

Objective Overview

Data Methodology and Measurement

Evidence-Based Resources

Add to Custom List

Status: Baseline only

Learn more about our data release schedule

Increase the proportion of adults who receive a colorectal cancer screening based on the most recent guidelines

Baseline: 65.2 percent of adults aged 50 to 75 years received a colorectal cancer screening based on the most recent guidelines in 2018 (age adjusted to the year 2000 standard population)

Target: 74.4 percent

Target Setting Method: Percentage point improvement

Data Source: National Health Interview Survey (NHIS), CDC/NCHS

Learn more about data measurement for this objective

Summary

Colorectal cancer is one of the most common causes of cancer deaths in the United States — and rates of colorectal cancer are higher in minority populations. Different screening methods can find colorectal cancer early and help prevent deaths. Interventions involving at least 2 approaches to colorectal cancer screening can help more adults get recommended screenings.

Topics: Cancer, Health Care, Health Care Access and Quality, Preventive Care

Workgroup: Cancer Workgroup

Other objectives you may be interested in

- Increase quality of life for cancer survivors — C-R01
- Increase the proportion of adults who get screened for lung cancer — C-03
- Increase the proportion of females at increased risk who get genetic counseling for breast and/or ovarian cancer — C-D01
- Increase the proportion of females who get screened for breast cancer — C-05
- Increase the proportion of females who get screened for cervical cancer — C-09

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This microsite is coordinated by the Office of Disease Prevention and Health Promotion, Office of the Assistant Secretary for Health, Office of the Secretary, U.S. Department of Health and Human Services.

ODPHP

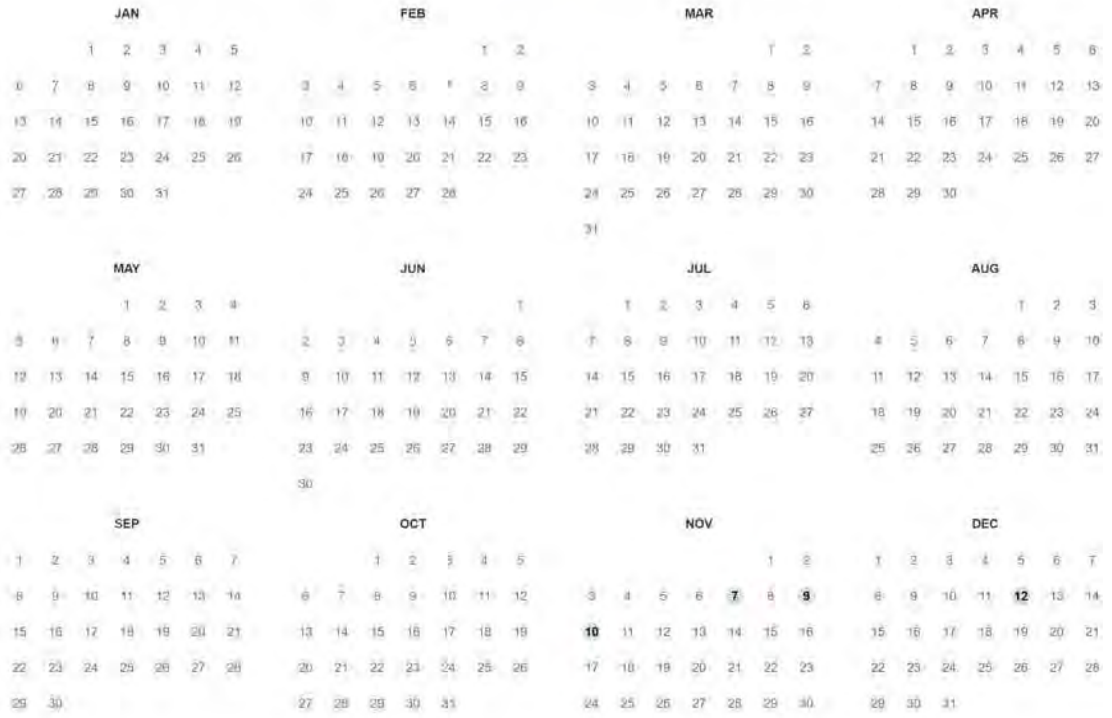
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Vital Signs

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Colorectal Cancer Tests Save Lives

The best test is the test that gets done
November 2013

CDC Vitalsigns™



90%
About 90% of people live 5 or more years when their colorectal cancer is found early through testing.

1 in 3
About 1 in 3 adults (23 million) between 50 and 75 years old is not getting tested as recommended.

1 in 10
10% of adults who got tested for colorectal cancer used an effective at-home stool test.

Colorectal cancer (CRC) is the second leading cancer killer of men and women in the US, following lung cancer. The US Preventive Services Task Force (USPSTF) recommends three CRC screening tests that are effective at saving lives: colonoscopy, stool tests (guaiac fecal occult blood test-FOBT or fecal immunochemical test-FIT), and sigmoidoscopy (now seldom done).

Testing saves lives, but only if people get tested. Studies show that people who are able to pick the test they prefer are more likely to actually get the test done. Increasing the use of all recommended colorectal cancer tests can save more lives and is cost-effective.

To increase testing, doctors, nurses, and health systems can:

- Offer all recommended test options with advice about each.
- Match patients with the test they are most likely to complete.
- Work with public health professionals to:
  - Get more adults tested by hiring and training "patient navigators," who are staff that help people learn about, get scheduled for, and get procedures done like colonoscopy.
  - Create ways to make it easier for people to get FOBT/FIT kits in places other than a doctor's office, like giving them out at flu shot clinics or mailing them to people's homes.

Issue Details

Problem

Not enough people are getting tested as needed.

About 23 million adults have never been tested.

- The people less likely to get tested are Hispanics, those aged 50-64, men, American Indian or Alaska natives, those who don't live in a city, and people with lower education and income.
- People with lower education and income are less likely to get tested.
- About 2 of every 3 adults who have never been tested for CRC actually have a regular doctor and health insurance that could pay for the test. Providers and patients do not always know about or consider all of the available tests.
- The three main tests–colonoscopy, FOBT/FIT, and flexible sigmoidoscopy are all effective at finding cancer early.
- Doctors often recommend colonoscopy more than other tests. Scientific studies have shown that many people would prefer FOBT/FIT if their health care provider gave them that option.

Currently, most health care providers and systems are not set up to help more people get tested.

- Many people do not know they need to be tested and are not notified when it is time for them to be tested.
- Most health care systems rely on doctors to remember to offer CRC tests to their patients. Nurses and other office staff should also talk with patients about getting tested and doctors can be reminded to offer CRC testing whenever patients are

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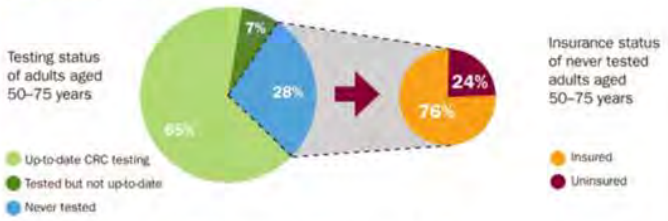
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due, whether they come in for a routine check-up or when they are sick.

- Health systems can make testing easier by:
  - Mailing out FOBT/FIT kits that can be completed by the person at home and mailed back, then making sure everyone with a test that is not normal promptly gets a colonoscopy.
  - Using a patient navigator to explain how to prepare for the test, how the test is done and to make sure people get to their appointments.

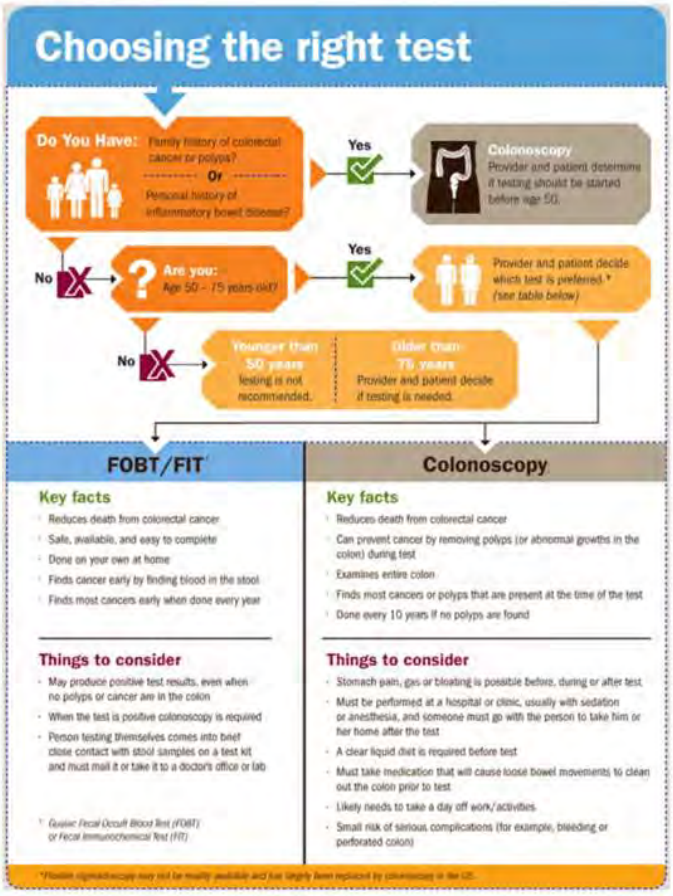
Many adults are not being tested

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SOURCE: Behavioral Risk Factor Surveillance System, 2012

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SOURCE: Vital Signs 2013 and USPSTF

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Appendix EXACT03



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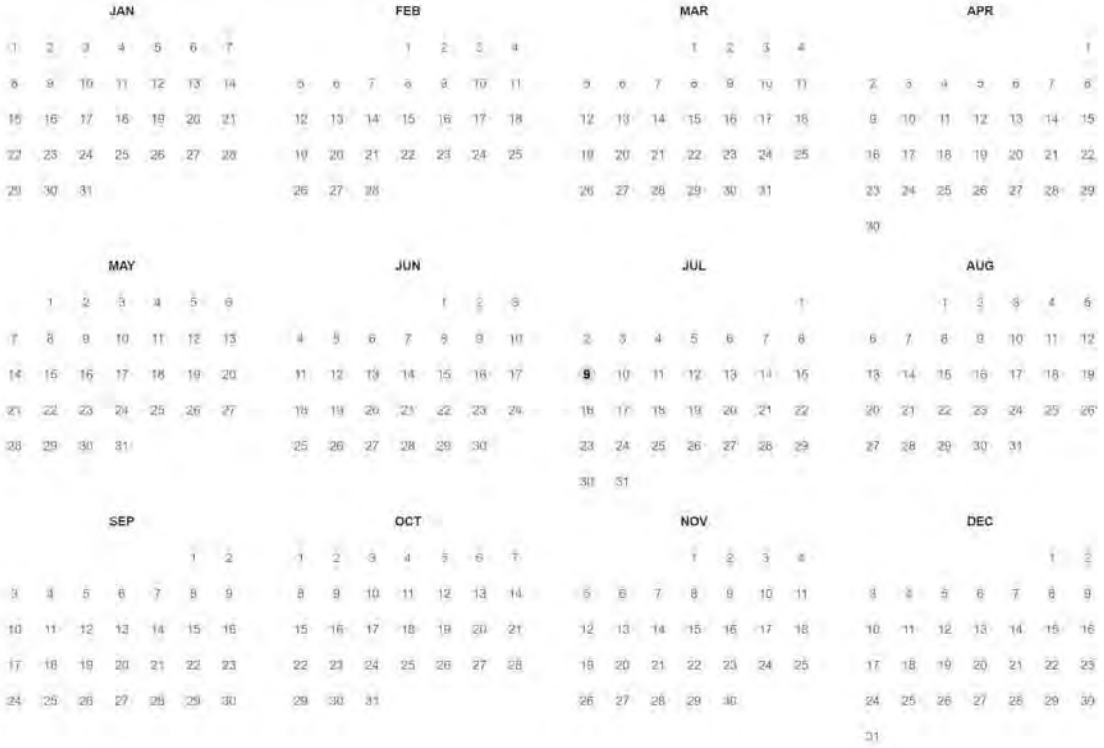
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Latest News

EXACT SCIENCES' COLOGUARD WINS PRESTIGIOUS PRIX GALIEN AWARD FOR BEST MEDICAL TECHNOLOGY PRODUCT

October 28, 2016 / by **Exact Sciences**

prixgalienlogo.png

MADISON, Wis., Oct. 28, 2016 /PRNewswire/ -- Exact Sciences Corp. (NASDAQ: EXAS) today announced that Cologuard, the first and only FDA-approved noninvasive, stool DNA-based colorectal cancer screening test, has won the 2016 10th Annual Prix Galien USA Award for best medical technology product. Awarded by the Galien Foundation, the Prix Galien USA awards are among the nation's highest honors recognizing biomedical and technology product achievement associated with improving the human condition.

"It's an extraordinary honor for Cologuard and the Exact Sciences team to be recognized in such a distinguished forum," said Graham Lidgard, Ph.D., chief science officer of Exact Sciences. "This Prix Galien award highlights not only the breakthrough science behind Cologuard, but also the unrivaled team that worked to develop and bring to market an innovation with the potential to make a significant impact in eradicating colorectal cancer. We are humbled and thankful to be counted among the companies honored by the Galien Foundation."

Awarded in more than a dozen countries, the Prix Galien awards recognize the best in biomedical research and development. Nominees for the Prix Galien USA awards represent the most innovative biopharma and medical technologies addressing public health priorities and are evaluated by a prestigious committee comprised of nine renowned leaders from the biomedical industry and academia, including four Nobel Laureates.

The awards were presented at the Prix Galien USA Awards Ceremony, which took place on Oct. 27 at the American Museum of Natural History in New York.

prixgaliengroup.jpg

The Exact Sciences and Mayo Clinics team at the Prix Galien USA Awards Ceremony Oct. 27 in New York

About the Galien Foundation

The Galien Foundation fosters, recognizes and rewards excellence in scientific innovation to improve the state of human health. Our vision is to be the catalyst for the development of the next generation of innovative treatment and technologies that will impact human health and save lives.

The Foundation oversees and directs activities in the USA for the Prix Galien, an international award that recognizes outstanding achievements in improving the human condition through the development of innovative therapies. The Prix Galien was created in France in 1970 in honor of Galen, the father of medical science and modern pharmacology. Worldwide, the Prix Galien is regarded as the equivalent of the Nobel Prize in biopharmaceutical and medical technology research.

For more information, visit www.galienfoundation.org.

About Cologuard

Archives

June 2017 (3)
May 2017 (1)
April 2017 (2)
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NONINVASIVE TEST FOR COLON CANCER SCREENING.
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Cologuard was approved by the FDA in August 2014 and results from Exact Sciences' prospective 90-site, point-in-time, 10,000-patient pivotal trial were published in the *New England Journal of Medicine* in March 2014. Cologuard is included in the recommendations of the U.S. Preventive Services Task Force (2016) and the American Cancer Society's (2014) colorectal cancer screening guidelines. Stool DNA is included in the combined screening guidelines of the American Cancer Society/U.S. Multi-Society Task Force/American College of Radiology (2008), the American College of Gastroenterology guidelines (2009) and the National Comprehensive Cancer Network (2016). Cologuard is indicated to screen adults of either sex, 50 years or older, who are at average risk for colorectal cancer. Cologuard is not for everyone and is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high-risk individuals. False positives and false negatives do occur. Any positive test result should be followed by a diagnostic colonoscopy. Following a negative result, patients should continue participating in a screening program at an interval and with a method appropriate for the individual patient. Cologuard performance when used for repeat testing has not been evaluated or established. For more information about Cologuard, visit www.CologuardTest.com. Rx Only.

About Exact Sciences Corp.
Exact Sciences Corp. is a molecular diagnostics company focused on the early detection and prevention of the deadliest forms of cancer. The company has exclusive intellectual property protecting its non-invasive, molecular screening technology for the detection of colorectal cancer. For more information, please visit the company's website at www.exactsciences.com, follow Exact Sciences on Twitter @ExactSciences or find Exact Sciences on Facebook.

This news release contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, that are intended to be covered by the "safe harbor" created by those sections. Forward-looking statements, which are based on certain assumptions and describe our future plans, strategies and expectations, can generally be identified by the use of forward-looking terms such as "believe," "expect," "may," "will," "should," "could," "seek," "intend," "plan," "estimate," "anticipate" or other comparable terms. All statements other than statements of historical facts included in this news release regarding our strategies, prospects, financial condition, operations, costs, plans and objectives are forward-looking statements. Examples of forward-looking statements include, among others, statements we make regarding expected future operating results, anticipated results of our sales and marketing efforts, expectations concerning payor reimbursement and the anticipated results of our product development efforts. Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based only on our current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, projections, anticipated events and trends, the economy and other future conditions. Because forward-looking statements relate to the future, they are subject to inherent uncertainties, risks and changes in circumstances that are difficult to predict and many of which are outside of our control. Our actual results and financial condition may differ materially from those indicated in the forward-looking statements. Therefore, you should not rely on any of these forward-looking statements. Important factors that could cause our actual results and financial condition to differ materially from those indicated in the forward-looking statements include, among others, the following: our ability to successfully and profitably market our products and services; the acceptance of our products and services by patients and healthcare providers; the willingness of health insurance companies and other payors to cover Cologuard and reimburse us for our performance of the Cologuard test; the amount and nature of competition from other cancer screening products and services; the effects of any healthcare reforms, including the Affordable Care Act, or changes in healthcare pricing, coverage and reimbursement; recommendations, guidelines and quality metrics issued by various organizations such as the U.S. Preventive Services Task Force, the American Cancer Society, and the National Committee for Quality Assurance regarding cancer screening or our products and services; our ability to successfully develop new products and services; our success establishing and maintaining collaborative, licensing and supplier arrangements; our ability to maintain regulatory approvals and comply with applicable regulations; and the other risks and uncertainties described in the Risk Factors and in Management's Discussion and Analysis of Financial Condition and Results of Operations sections of our most recently filed Annual Report on Form 10-K and our subsequently filed Quarterly Report(s) on Form 10-Q. We undertake no obligation to publicly update any forward-looking statement, whether written or oral, that may be made from time to time, whether as a result of new information, future developments or otherwise.

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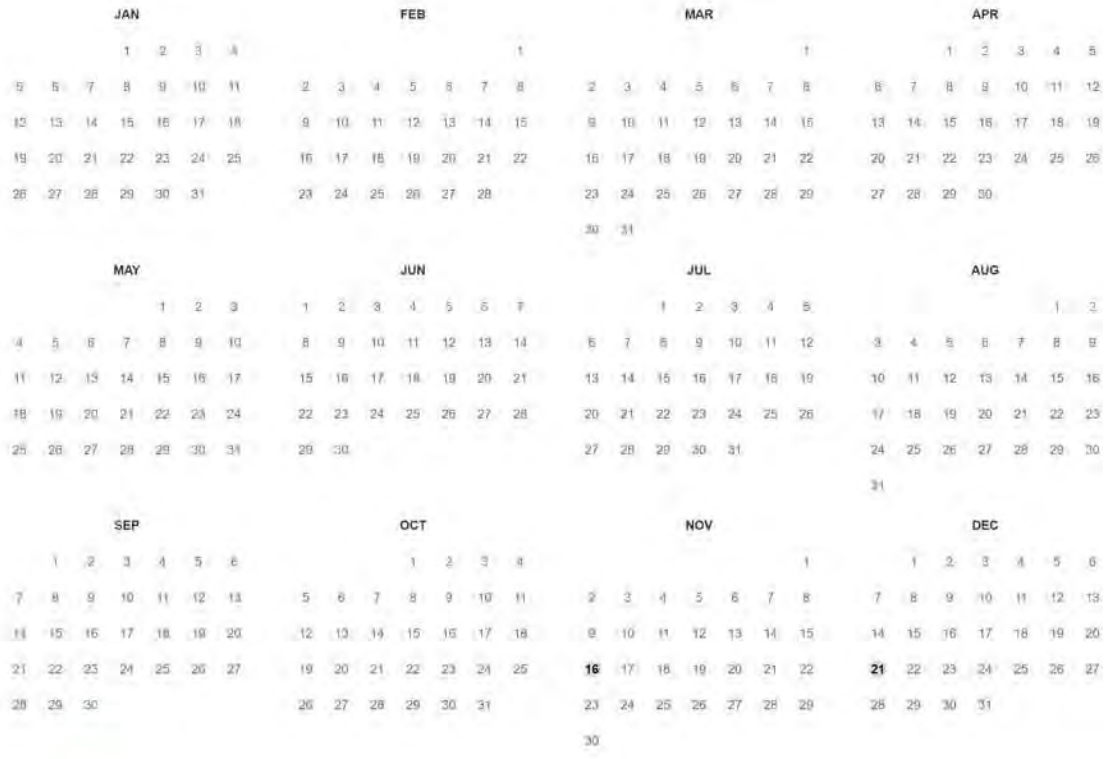
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COLOGUARD® WINS POPULAR SCIENCE MAGAZINE'S 2014 "BEST OF WHAT'S NEW" AWARD

November 12, 2014 / by **Exact Sciences**

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NEW **NONINVASIVE** TEST FOR **COLON CANCER SCREENING.**
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Exact Sciences' new colon cancer screening test recognized as a revolution in healthcare

MADISON, Wis.--(BUSINESS WIRE)-- Exact Sciences Corp. (NASDAQ: EXAS) today announced Cologuard has received a 2014 "Best of What's New" award from *Popular Science*.

Cologuard is the first and only FDA-approved noninvasive stool DNA screening test for colorectal cancer. Approved by the FDA in August, Cologuard detects the presence of cancer and precancer by analyzing both DNA and blood in the stool.

"Exact Sciences is honored to receive this recognition from the editors of *Popular Science*," said Kevin Conroy, Chairman and CEO of Exact Sciences. "The 'Best of What's New' list recognizes the groundbreaking potential of Cologuard to improve the colon cancer screening rates and enable survival from a disease that is often considered the most preventable, yet least prevented cancer due to the lack

of patient compliance with screening."

Colorectal cancer is highly treatable with early detection through screening. However, 23 million Americans between 50 and 75 are not getting screened as recommended and, as a result, colorectal cancer remains the second-leading cancer killer in the United States. For those whose cancer is detected at an earlier stage, the five-year survival rate can be greater than 90 percent.

Cologuard, which is available by prescription, offers people 50 years and older, who are at average risk for colorectal cancer, an easy to use screening test, which they can do in the privacy of their own home. Cologuard has been proven to find 92 percent of colorectal cancers in average risk patients with 87 percent specificity. Cologuard does not require medication, dietary restrictions or bowel preparation prior to taking the test. It is the first noninvasive screening test for colorectal cancer that analyzes both stool-based biomarkers including DNA and blood to detect cancer and precancer.

Each year, editors of *Popular Science* review thousands of new products and innovations of the year and choose the top 100 winners across 12 categories for inclusion in their annual "Best of What's New" issue. To win, a product or technology must represent a significant step forward in its category. All of the winners are featured on the *Popular Science* website, and in the special *Popular Science* December issue, on newsstands today.

About Exact Sciences Corp.

Exact Sciences Corp. (NASDAQ: EXAS) is a molecular diagnostics company focused on the early detection and prevention of colorectal cancer. The company has exclusive intellectual property protecting its noninvasive, molecular screening technology for the detection of colorectal cancer. Stool DNA technology is included in the colorectal cancer screening guidelines of the American Cancer Society and the U.S. Multi-Society Task Force on Colorectal Cancer. For more information, , follow us on Twitter @ExactSciences or find us on Facebook.

Rx only.

About Popular Science

Founded in 1872, Popular Science is the world's largest science and technology magazine; with a circulation of 1.3 million and 6.8 million monthly readers. Each month, Popular Science reports on the intersection of science and everyday life, with an eye toward what's new and why it matters. Popular Science is published by Bonnier Active Media, a subsidiary of Bonnier Corporation.

Certain statements made in this news release contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities and Exchange Act of 1934, as amended that are intended to be covered by the "safe harbor" created by those sections. Forward-looking statements, which are based on certain assumptions and describe our future plans, strategies and expectations, can generally be identified by the use of forward-looking terms such as "believe," "expect," "may," "will," "should," "could," "seek," "intend," "plan," "estimate," "anticipate" or other comparable terms.Forward-looking statements in this news release may address the following subjects among others: statements regarding the sufficiency of our capital resources, our ability to secure favorable reimbursement rates from Medicare and other third-party payors, timing of our launch of a commercial product, our estimates of the available market size and our potential penetration, expected research and development expenses, expected general and administrative expenses and our expectations concerning our business strategy. Forward-looking statements involve inherent risks and uncertainties which could cause actual results to differ materially from those in the forward-looking statements, as a result of various factors including those risks and uncertainties described in the Risk Factors and in Management's Discussion and Analysis of Financial Condition and Results of Operations sections of our most recently filed Annual Report on Form 10-K and our subsequently filed Quarterly Reports on Form 10-Q. We urge you to consider those risks and uncertainties in evaluating our forward-looking statements. We caution readers not to place undue reliance upon any such forward-looking statements, which speak only as of the date made. Except as otherwise required by the federal securities laws, we disclaim any obligation or undertaking to publicly release any updates or revisions to any forward-looking statement contained herein (or elsewhere) to reflect any change in our expectations with regard thereto or any change in events, conditions or circumstances on which any such statement is based.

Photos/Multimedia Gallery
Available: http://www.businesswire.com/multimedia/home/20141112006429/en/

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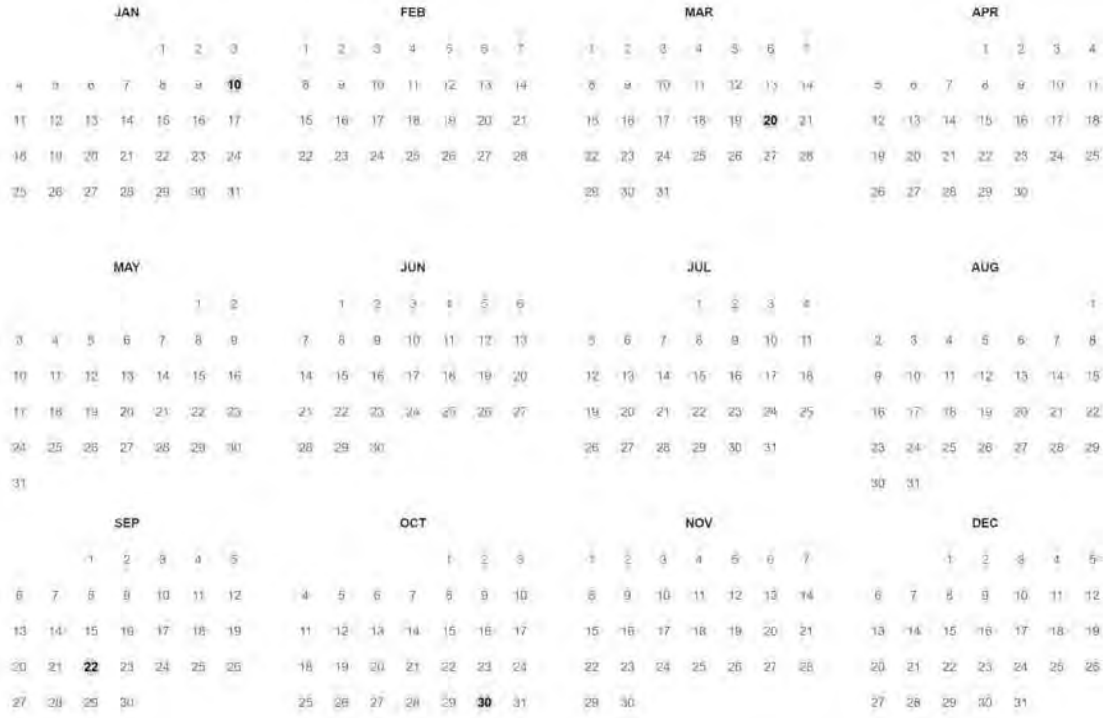
Appendix PRNEWS01

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18 captures 10 Jan 2015 - 3 Oct 2023

Everyday Health Awards for Innovation Winners Announced at 2015 International CES®

Leading Pioneers Honored for Outstanding Technology Innovations in Digital Health

Share

LAS VEGAS, Jan. 7, 2015 /PRNewswire/ -- Everyday Health, Inc., a leading provider of digital health and wellness solutions, announced today the winners for the 2nd Annual Everyday Health Awards for Innovation. The winners were honored at a live award ceremony at the Digital Health Summit, presented by Living in Digital Times, at the 2015 International CES®.

"These awards continue to bring the most inventive and creative digital health technologies and services to the forefront," said Paul Slavin, Executive Vice President and Chief Operating Officer of Everyday Health, Inc. "Each of the winners demonstrated an incredible understanding about where the digital health marketplace is going and how we can propel it forward."

"We are so fortunate that these awards can be showcased at CES, where consumers, developers and companies can come together to understand and appreciate what these digital health innovations will mean for everyone," said Jill Gilbert, producer of the Digital Health Summit. "The winners have displayed an innate ability to look at the marketplace and really evaluate what technologies and services are missing from the digital healthcare arena."

The winners are:

Personal Health:

- STEMP™

Chronic Condition Management:

- Quikiks™

Healthiest Company:

- Virgin Pulse

Healthy Aging:

- SingFit PRIME

Pet Health:

- LifeLearn Sofie™

Student Innovation:

- @HomeVitals™

Emerging Tech:

- Cologuard®

Audience Favorite:

- HealthTap
- LifeLearn Sofie™

The Everyday Health Awards for Innovation honor the latest technologies and services dedicated to improving overall health and wellbeing. Finalists were chosen from a panelist of expert judges and the winners were selected through a combination of those judges and popular online votes. The Audience Favorite was determined by votes cast at Awards.DigitalHealthSummit.com . A selection of the winners and finalists will be showcased in the Health & Wellness marketplace exhibit (Everyday Health booth #73035 at Sands Expo, Level 2) at CES until January 9.

For updates, follow Digital Health Summit on Twitter @dhsummit "like" Digital Health Summit on Facebook and follow the hashtag #EHawardsCES.

About Everyday Health, Inc.

Everyday Health, Inc. (NYSE: EVDY) is a leading provider of digital health and wellness solutions. Everyday Health attracts a large and engaged audience of consumers and healthcare professionals to its premier health and wellness properties, and utilizes its data and analytics expertise to deliver highly personalized content experiences and efficient and effective marketing and engagement solutions. Everyday Health enables consumers to manage their daily health and wellness needs, healthcare professionals to stay informed and make better decisions for their patients, and marketers, health payors and providers to communicate and engage with consumers and healthcare professionals to drive better health outcomes. Everyday Health's content and solutions are delivered through multiple channels, including desktop, mobile web, and mobile phone and tablet applications, as well as video and social media.

Media Contacts:

Linda Krebs/Sarah Gartner
LKPR, Inc. for Living in Digital Times
LK@LKPublicRelations.com / Sarah@LkPublicRelations.com
646-484-4539/631-327-6307

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WhatToExpect.com Announces Second Annual "Moms Love-It" Award Winners for Top Baby Registry Items
Jan 08, 2015, 08:00 ET

Everyday Health to Present at Upcoming Investor Conferences
Dec 22, 2014, 16:01 ET

Everyday Health to Present at Upcoming Conferences
Nov 19, 2014, 08:30 ET

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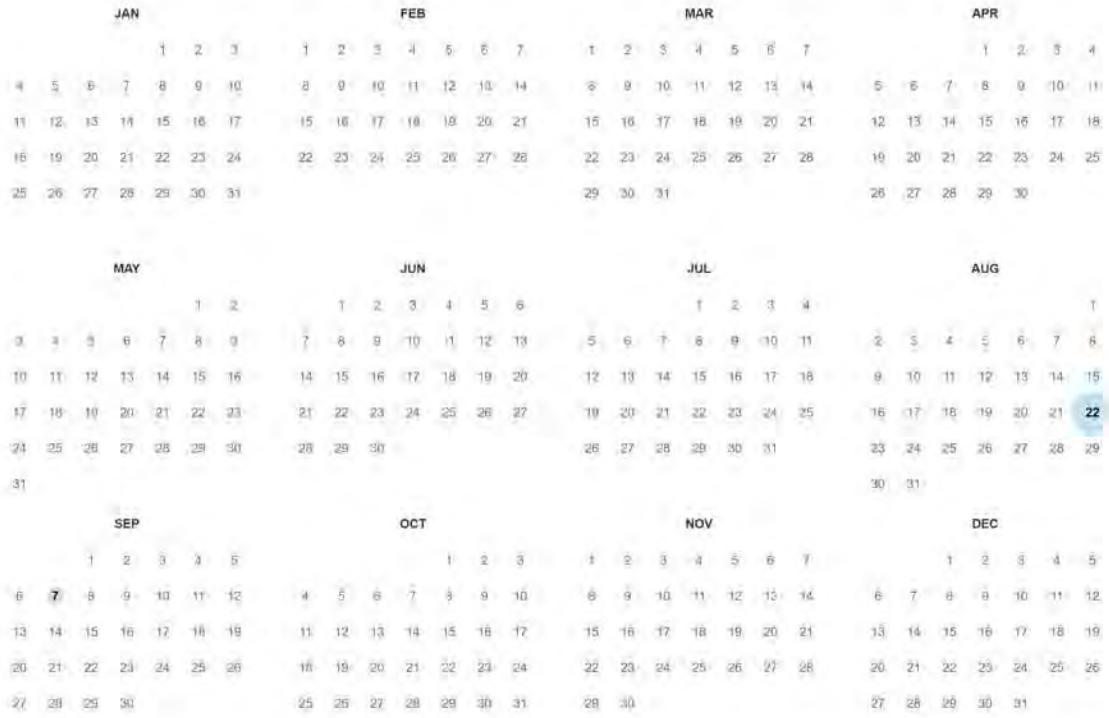
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Latest News

EXACT SCIENCES WINS WISCONSIN INNOVATION AWARD

August 19, 2015 / by **Exact Sciences**



Cologuard® recognized as a leading innovation in the state

MADISON, Wis.--(BUSINESS WIRE)-- Exact Sciences Corp. (NASDAQ: EXAS) today announced that Cologuard was awarded a Wisconsin Innovation Award (WIA) in the "Healthcare/Health IT" category at the second annual ceremony held on August 18, 2015 at Discovery World in Milwaukee, Wisconsin. Cologuard was chosen from more than 170 entries and 33 finalists to receive one of 10 awards.

"Cologuard is an innovative test for the early detection of colon cancer that provides patients with an easy-to-use and noninvasive screening option," said Kevin Conroy, Chairman and CEO of Exact Sciences. "The uniqueness of Cologuard is indicative of the creativity, ingenuity and collaboration taking place throughout Wisconsin. We are honored to be recognized with this award and remain committed to achieving our mission of helping eradicate colon cancer through early detection."

Cologuard is the first and only FDA approved noninvasive stool DNA screening test for colorectal cancer. It detects the presence of cancer and precancer by analyzing both DNA and blood in the stool and offers people an easy-to-use screening test, which they can do in the privacy of their own home. Unlike other screening options, Cologuard does not require medication or dietary restrictions or bowel preparation prior to taking the test. Cologuard is available by prescription only through a healthcare provider.

Led by a steering committee of business, community and entrepreneurial leaders, the WIA hopes to encourage an even greater environment of innovation by bringing together leaders from various business sectors (e.g. tech, food, healthcare, agriculture, nonprofits, education, government) and from throughout the state of Wisconsin.

About Cologuard

Archives

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NONINVASIVE TEST FOR COLON CANCER SCREENING.
cologuard
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Cologuard was approved by the FDA in August 2014 and results from Exact Sciences' prospective 90-site, point-in-time, 10,000-patient pivotal trial were published in the *New England Journal of Medicine* in March 2014. Cologuard is included in the colorectal cancer screening guidelines of the American Cancer Society and stool DNA is listed in the screening guidelines of the U.S. Multi-Society Task Force on Colorectal Cancer.

Cologuard is indicated to screen adults of either sex, 50 years or older, who are at average risk for colorectal cancer. Cologuard is not for everyone and is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high-risk individuals. False positives and false negatives do occur. Any positive test result should be followed by a diagnostic colonoscopy. Following a negative result, patients should continue participating in a screening program at an interval and with a method appropriate for the individual patient. Cologuard performance when used for repeat testing has not been evaluated or established. For more information about Cologuard, visit www.CologuardTest.com. Rx Only.

About Exact Sciences

Exact Sciences Corp. (NASDAQ: EXAS) is a molecular diagnostics company focused on the early detection and prevention of colorectal cancer. The company has exclusive intellectual property protecting its noninvasive, molecular screening technology for the detection of colorectal cancer. For more information, please follow us on Twitter @ExactSciences or find us on Facebook.

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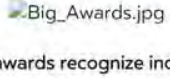
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10 Oct 2016 - 30 Jul 2019

Latest News

EXACT SCIENCES HONORED AS 2016 BIG AWARD COMPANY OF THE YEAR IN HEALTH CARE

October 6, 2016 / by Exact Sciences



Annual Business Intelligence Group (BIG) awards recognize industry leadership and performance

MADISON, Wis., Oct. 6, 2016 – Exact Sciences Corp. (Nasdaq: EXAS) today announced that the company received the Business Intelligence Group's 2016 Company of the Year BIG Award for Business in the Health Care category.

The BIG Awards were launched in 2012 to recognize and reward companies, products and people that are leading their respective industries, as judged by business executives.

"We are honored to receive this year's BIG Award, which recognizes the tireless efforts of our entire team to develop Cologuard and position it to become a standard of care in colon cancer screening," said Kevin Conroy, chairman and CEO of Exact Sciences. "Since inception, we have focused on a single goal: helping win the war on cancer through early detection. Cologuard represents an important step toward reaching that goal. Thank you to the judges and the Business Intelligence Group for this recognition and congratulations to our fellow recipients for their achievements."

In 2014, following nearly 20 years of research and development, Exact Sciences launched Cologuard®, the first and only FDA-approved, stool DNA-based screening test for adults 50 and older who are at average risk for colorectal cancer. Colon cancer is considered one of the most preventable cancers because of the extended period of time for precancer to develop into cancer. However, it's also considered one of the least prevented cancers because more than 41 percent of Americans ages 50-75 are unscreened. Since FDA approval of Cologuard, Exact Sciences remains focused on increasing the colon cancer screening population by expanding patient access to this innovative test.

"The Business Intelligence Group highlights those with vision, creativity and persistence, all hallmarks found in the world's leading companies and individuals across the globe," said Russ Fordyce, managing director of the Business Intelligence Group. "Exact Sciences—in its journey to bring to market, drive awareness of and expand access to a game changer in colon cancer screening—exemplifies all of these qualities. We congratulate Exact Sciences and all of this year's winners, as they are truly a select group."

About Cologuard

Cologuard was approved by the FDA in August 2014 and results from Exact Sciences' prospective 90-site, point-in-time, 10,000-patient pivotal trial were published in the *New England Journal of Medicine* in March 2014. Cologuard is included in the recommendations of the U.S. Preventive Services Task Force (2016) and the American Cancer Society's (2014) colorectal cancer screening guidelines. Stool DNA is included in the combined screening guidelines of the American Cancer Society/U.S. Multi-Society Task Force/American College of Radiology (2008), the American College of Gastroenterology guidelines (2009) and the National Comprehensive Cancer Network (2016). Cologuard is indicated to screen adults of either sex, 50 years or older, who are at average risk for colorectal cancer. Cologuard is not for everyone and is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high-risk individuals. False positives and false negatives do occur. Any positive test result should be followed by a diagnostic colonoscopy. Following a negative result, patients should continue participating in a

Archives
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screening program at an interval and with a method appropriate for the individual patient. Cologuard performance when used for repeat testing has not been evaluated or established. For more information about Cologuard, visit www.CologuardTest.com. Rx Only.

About Exact Sciences Corp.

Exact Sciences Corp. is a molecular diagnostics company focused on the early detection and prevention of the deadliest forms of cancer. The company has exclusive intellectual property protecting its non-invasive, molecular screening technology for the detection of colorectal cancer. For more information, please visit the company's website at www.exactsciences.com, follow Exact Sciences on Twitter @ExactSciences or find Exact Sciences on Facebook.

About Business Intelligence Group

The Business Intelligence Group was founded with the mission of recognizing true talent and superior performance in the business world. Unlike other industry award programs, business executives—those with experience and knowledge—judge the programs. The organization's proprietary and unique scoring system selectively measures performance across multiple business domains and then rewards those companies whose achievements stand above those of their peers. For more information, please visit: www.bintelligence.com.

This news release contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended that are intended to be covered by the "safe harbor" created by those sections. Forward-looking statements, which are based on certain assumptions and describe our future plans, strategies and expectations, can generally be identified by the use of forward-looking terms such as "believe," "expect," "may," "will," "should," "could," "seek," "intend," "plan," "estimate," "anticipate" or other comparable terms. All statements other than statements of historical facts included in this news release regarding our strategies, prospects, financial condition, operations, costs, plans and objectives are forward-looking statements. Examples of forward-looking statements include, among others, statements we make regarding expected future operating results, anticipated results of our sales and marketing efforts, expectations concerning payor reimbursement and the anticipated results of our product development efforts. Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based only on our current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, projections, anticipated events and trends, the economy and other future conditions. Because forward-looking statements relate to the future, they are subject to inherent uncertainties, risks and changes in circumstances that are difficult to predict and many of which are outside of our control. Our actual results and financial condition may differ materially from those indicated in the forward-looking statements. Therefore, you should not rely on any of these forward-looking statements. Important factors that could cause our actual results and financial condition to differ materially from those indicated in the forward-looking statements include, among others, the following: our ability to successfully and profitably market our products and services; the acceptance of our products and services by patients and healthcare providers; the willingness of health insurance companies and other payors to cover Cologuard and reimburse us for our performance of the Cologuard test; the amount and nature of competition from other cancer screening products and services; the effects of any healthcare reforms, including the Affordable Care Act, or changes in healthcare pricing, coverage and reimbursement; recommendations, guidelines and/or quality metrics issued by various organizations such as the U.S. Preventive Services Task Force, the American Cancer Society and the National Committee for Quality Assurance regarding cancer screening or our products and services; our ability to successfully develop new products and services; our success establishing and maintaining collaborative, licensing and supplier arrangements; our ability to maintain regulatory approvals and comply with applicable regulations; and the other risks and uncertainties described in the Risk Factors and in Management's Discussion and Analysis of Financial Condition and Results of Operations sections of our most recently filed Annual Report on Form 10-K and our subsequently filed Quarterly Report(s) on Form 10-Q. We undertake no obligation to publicly update any forward-looking statement, whether written or oral, that may be made from time to time, whether as a result of new information, future developments or otherwise.

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550			a| Official journal of: the American College of Preventive Medicine; and: the Association of Teachers of Preventive Medicine.
650		0	a| Medicine, Preventive v| Periodicals.
650		0	a| Public health v| Periodicals.
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650		2	a| Preventive Medicine.
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710	2		a| American College of Preventive Medicine.
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936			a| Vol. 7, no. 2 (Mar./Apr. 1991) LIC
949			a| RA421.A4 v.20 2001 & suppls. w| LCPER c| 1 i| 000048238281 d| 10/10/2000 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 4/13/2001
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949			a| RA421.A4 v.22 2002 & suppl. w| LCPER c| 1 i| 000048433051 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 11/14/2002
949			a| RA421.A4 v.23 2002 & suppls. w| LCPER c| 1 i| 000051697655 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 3/13/2003
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949			a| RA421.A4 v.2 1986 w| LCPER c| 1 i| 000073914457 d| 7/12/2023 l| PATERNO-4 m| UP-PAT q| 1 r| Y s| Y t| PERIODICAL u| 1/24/2013
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949			a| RA421.A4 v.5 1989 w| LCPER c| 1 i| 000073914488 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 1/24/2013
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949			a| RA421.A4 v.9 no.1-3 1993 & suppl. w| LCPER c| 1 i| 000073914525 l| PATERNO-4 m| UP-PAT r| Y s| Y t| PERIODICAL u| 1/24/2013
949			a| RA421.A4 v.9 no.4-6 1993 & suppl. w| LCPER c| 1 i| 000073914433 d| 2/22/2023 l| PATERNO-4 m| UP-PAT q| 5 r| Y s| Y t| PERIODICAL u| 1/24/2013
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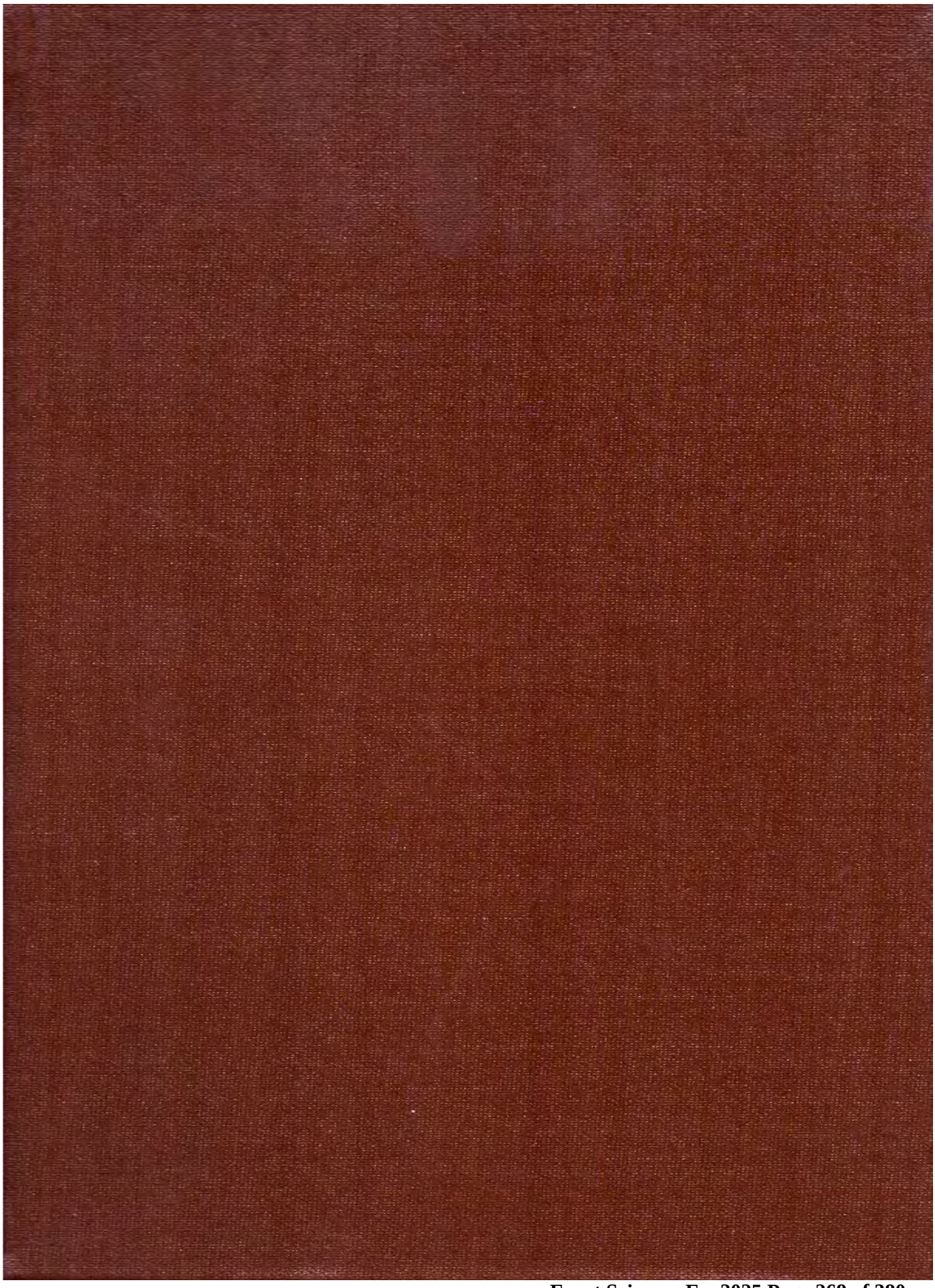
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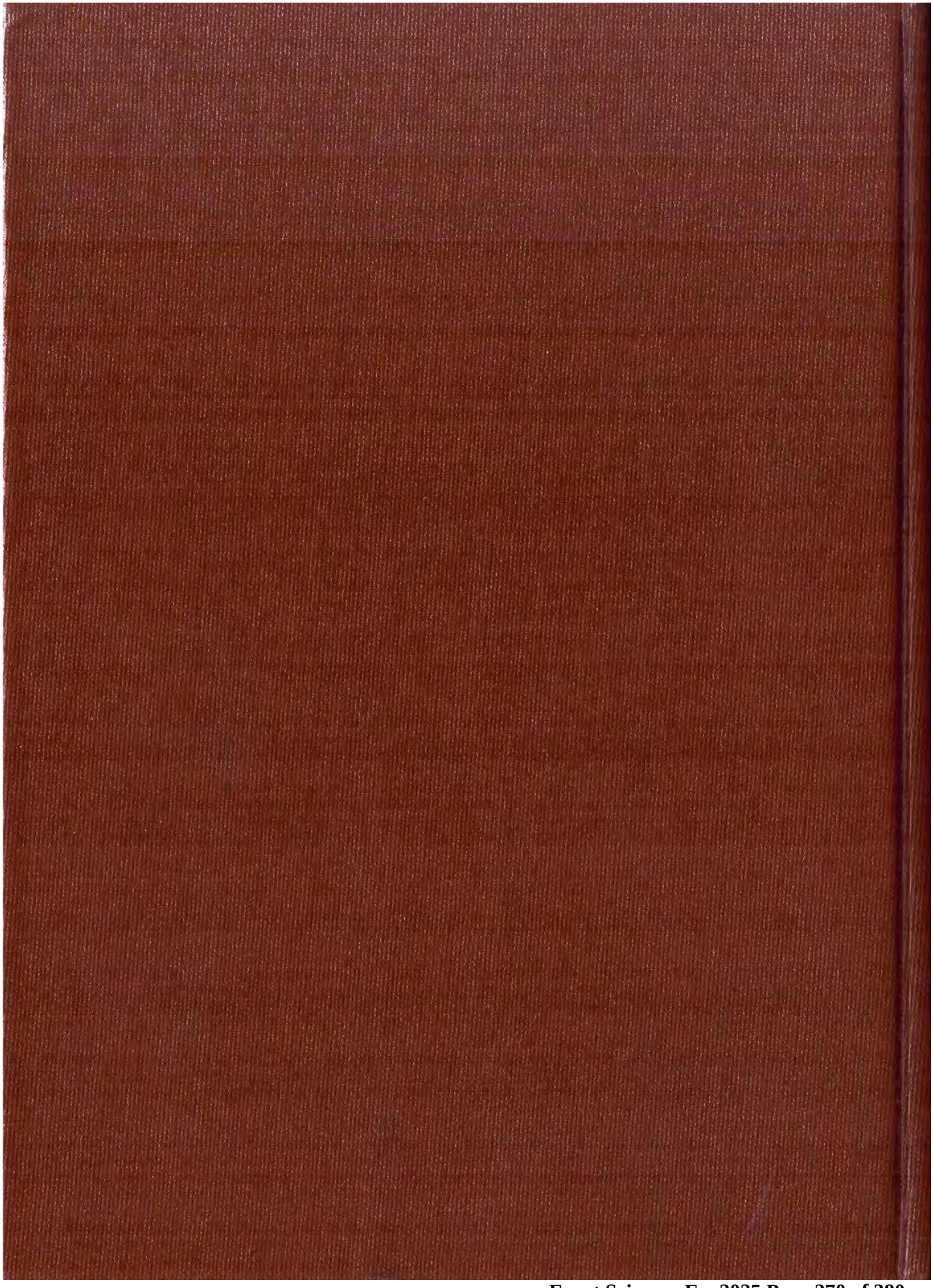


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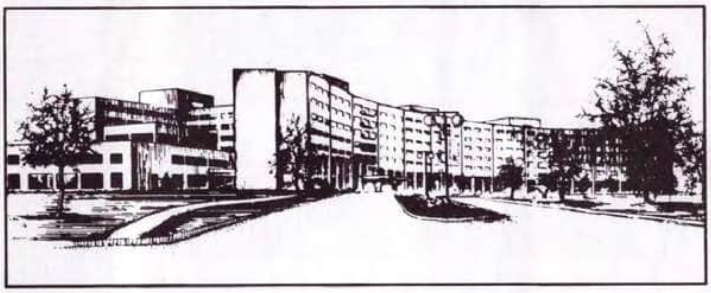
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Patient Perceptions of Stool-Based DNA Testing for Colorectal Cancer Screening

Paul C. Schroy III, MD, MPH, Timothy C. Heeren, PhD

Purpose: Stool-based DNA (SB-DNA) testing is an emerging colorectal cancer screening strategy that offers a convenient, noninvasive, and potentially more acceptable alternative to existing screening tests. The objectives of this study were to compare patient perceptions of SB-DNA testing, fecal occult blood testing (FOBT), and colonoscopy, and elicit screening preferences.

Methods: A prospective survey was conducted between August 2001 and March 2003 of asymptomatic, mostly average-risk subjects aged ≥50 years who were participating in a multicenter comparison of SB-DNA testing and FOBT for detecting colorectal neoplasia. Subjects completed a 25-item questionnaire within 48 hours after undergoing a colonoscopy, which served as the standard. Respondents were asked to rate each of the three screening tests on various prep- and test-related features, using a five-point ordinal scale or yes/no format, and to select a preferred strategy.

Results: A total of 4042 subjects completed the survey (84% response rate). SB-DNA testing received the same or higher mean ratings than FOBT for most prep- and test-related features. When compared with colonoscopy, SB-DNA testing received higher ratings for all prep- and test-related features except perceived accuracy, where colonoscopy was rated higher. Overall, a higher percentage of patients preferred SB-DNA testing (45%) to both FOBT (32%) and colonoscopy (15%) for routine screening ($p<0.001$); 8% had no preference.

Conclusions: Patients willing to undergo colonoscopy, SB-DNA testing, and FOBT perceive SB-DNA testing to have a number of advantages over the other two tests. Moreover, many such patients prefer SB-DNA testing to FOBT and colonoscopy for routine screening.
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Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related death and fourth most commonly diagnosed cancer among men and women in the United States.[1] Over the past decade, sufficient evidence has accumulated to suggest that screening is a cost-effective strategy for reducing both CRC incidence and mortality.[2] Consequently, most authoritative groups now endorse screening for both average and high-risk patients.[3–6] Despite a compelling rationale and widespread endorsement by authoritative groups, however, screening rates remain far below those necessary to achieve significant reductions in CRC mortality or incidence.[7,8]

Poor patient adherence has been a major barrier to CRC screening. Previous studies have identified practical reasons (e.g., conflicts with work or family commitments, inconvenience, lack of interest, and cost), lack of current health problems or worrisome symptoms, and most importantly, lack of a physician recommendation as the major reasons for nonparticipation.[9,10] Negative attitudes toward the tests themselves are also prevalent. Fecal occult blood testing (FOBT) is widely perceived as embarrassing or distasteful, whereas concerns about pain, discomfort, and injury are common for sigmoidoscopy and colonoscopy.[9,10] Lack of confidence to complete the tests (i.e., lack of self-efficacy), anxiety about the consequences of screening (e.g., the need for further testing or a cancer diagnosis), and inconsistent or inadequate support from friends, family, media, and insurers are other frequently cited reasons for nonparticipation.[9,10]

Stool-based DNA testing is a novel screening strategy that offers a convenient, noninvasive alternative to existing screening tests. Like FOBT, stool-based DNA testing can potentially detect neoplasia anywhere in the large bowel with sample collection that can be performed at home. Unlike FOBT, however, no dietary or medication restrictions are required and the sample can be collected using a specialized device that obviates the need for

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handling stool. Published studies to date suggest that stool-based DNA testing with a commercially available multitarget assay—which detects 21 point mutations in the K-*ras* proto-oncogene or APC and p53 tumor suppressor genes, a microsatellite instability marker (BAT-26), and a marker of defective apoptosis ("long DNA")—has a sensitivity in the range of 62% to 91% for detecting colorectal cancers and 50% to 82% for advanced adenomas; specificity has been in the range of 93% to 100%.[11–14] These data would suggest that the performance of SB-DNA for detecting advanced colorectal neoplasia may be superior to FOBT (sensitivity ~24%; specificity ~94%),[15] but inferior to colonoscopy (sensitivity ~95%; specificity ~100%).[6] An equally important yet undefined issue relates to the question of whether stool-based DNA testing is acceptable to patients. Hence, the principal objective of this study was to assess and compare the perceptions of asymptomatic, mostly average-risk subjects undergoing stool-based DNA testing, FOBT, and colonoscopy as part of one of the large multicenter trials. A secondary objective was to elicit CRC screening preferences.

Methods

Survey Sample

The survey sample population comprised asymptomatic men and women aged ≥50 years who were participating in a multicenter comparison of SB-DNA (PreGen-Plus™, EXACT Sciences Corporation, Marlborough MA) and FOBT (Hemoccult® II, Beckman Coulter, Palo Alto CA) for detecting CRC neoplasia. Subjects were recruited through normal patient referral channels at each of the 84 participating U.S. sites, including 71 community-based practices and 13 academic centers, between August 2001 and March 2003. Newspaper advertising and distribution of pamphlets in doctors' offices were also employed at select study site areas to aid in subject recruitment. At the time of recruitment, patients were informed that the purpose of the study was to compare the sensitivities of SB-DNA and FOBT for detecting colorectal cancer, using colonoscopy as the standard; no additional information regarding individual test features or performance was provided. Patients meeting eligibility criteria were stratified on enrollment into three groups based on age: 50 to 54, 55 to 64, and ≥65 years. The goal was to recruit 250 subjects in the 50-to-54 age group, 750 in the 55-to-64 age group, and 4000 in the ≥65 age group to optimize the likelihood of detecting a sufficient number of cancers (n =35) to satisfy pre-study power determinations. Subjects received monetary honoraria for their participation, which varied in amount from $150 to $250, to cover incidental costs and inconveniences.

Potential subjects presenting with any of the following were deemed ineligible: any prior structural colorectal examination (i.e., colonoscopy, double-contrast barium, "virtual colonoscopy," or flexible sigmoidoscopy) within the past 10 years; personal history of colorectal neoplasia, familial adenomatous polyposis, or hereditary nonpolyposis colorectal cancer or inflammatory bowel disease; personal history of extracolonic cancers other than skin cancer diagnosed within the past 5 years; active gastrointestinal symptoms; two or more first-degree relatives with colorectal cancer; overt gastrointestinal bleeding within the past month; any positive FOBT within the past 6 months; medical conditions for which colonoscopy was contraindicated; anticoagulant use or coagulopathy; and current pregnancy or lactation. Patients at moderate risk because of a family history of colorectal cancer or polyps affecting a single first-degree relative aged ≥50 years were eligible.

Study Design

Consenting subjects were asked to submit a stool sample for SB-DNA testing, prepare three Hemoccult II cards for FOBT, and undergo a colonoscopy within 8 weeks of enrollment. For SB-DNA testing, subjects were instructed to collect a single whole stool using a plastic bucket-type container that could be mounted on the toilet seat and sealed with an airtight lid; samples were shipped directly from home using a courier service within 24 hours of collection. For FOBT, subjects were instructed to implement dietary restrictions specified by the manufacturer and discontinue use of aspirin and other nonsteroidal anti-inflammatory agents for ≥72 hours before collecting two smears from each stool on 3 consecutive days; once completed, the Hemoccult II were returned to the participating site for processing in a prepaid, pre-addressed envelope. Following submission of both the stool sample for SB-DNA testing and Hemoccult II cards for FOBT, subjects underwent colonoscopy after either a Fleet's phosphasoda or balanced-electrolyte, polyethylene-glycol bowel preparation, as recommended by their endoscopist. Apart from procedural instructions, subjects received no specific information regarding the various tests with respect to features such as discomfort, inconvenience, accuracy, or cost.

The study protocol was approved by the institutional review board or ethics committee at each participating site. Informed written consent was obtained from each patient.

Survey Process and Instrument

Subjects were asked to answer a brief questionnaire within 2 days of completing the colonoscopy. The questionnaire was composed of 25 items that asked respondents to rate each of the three screening tests on a variety of features related to the test preparation or test itself, using a five-point ordinal scale or yes/no format. Depending on the feature of interest, questions might relate to all three tests, any two of the three tests, or only a single test. Respondents were also asked to identify a preferred strategy for their "routine" CRC screening. The questionnaire was devoid of all identifiers other than a subject identification number to preserve subject confidentiality. Completed surveys were returned by mail in a prepaid envelope addressed to the contract research organization.

The initial survey instrument was generated in response to feedback from face-to-face interviews and focus groups involving >500 physicians (primary care physicians, gastroenterologists, medical oncologists, and gynecologists) and patients (previously screened and unscreened). The instrument was then reviewed for content validity by a clinical gastroenterologist, pilot tested on 147 patients, and revised before use.

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Table 1. Characteristics of study sample with linked demographic and response data (n = 3359)

Subgroup	n (%)
Gender	
Female	1921 (57.2)
Male	1438 (42.8)
Age (years)	
50–54	164 (4.9)
55–64	491 (14.6)
≥65	2704 (80.5)
Race/ethenicity	
White	3001 (89.3)
Nonwhite	358 (10.7)
Family history	
No	2880 (85.8)
Yes	479 (14.2)
Polyps detected[a]	
No	1772 (53.9)
Yes	1513 (46.1)
Cancer detected[a]	
No	3256 (99.1)
Yes	29 (0.9)

[a]Data missing for 75 subjects (2.2%).

Statistical Analyses

Respondents rated each of the three screening tests on a variety of prep- and test-related features using a five-point ordinal scale, with lower values indicating a more positive rating. To compare ratings, the mean (standard deviation [SD]) rating for each procedure was calculated and compared pairwise through nonparametric signed-rank tests to acknowledge the skewed nature of many of the response distributions (most respondents giving positive ratings). To control for multiple testing, Bonferroni adjustments to pairwise p values were used when reporting significance. Respondents were also asked to give an overall preference to one of the procedures. The percentage of patients preferring stool-based DNA testing, FOBT, or colonoscopy were compared for the overall sample and within subgroups, defined by patient characteristics, through pairwise chi-square goodness-of-fit tests with Bonferroni adjustments to account for multiple testing among the three procedures. Significance for all tests was defined at the two-tailed $p<0.05$ level. All data were analyzed using SAS, version 8 (SAS Institute Inc., Cary NC, 1999).

Results

Response Rate and Respondent Demographics

Eighty-four percent (4042 of 4840) of subjects who completed each of the three screening tests, or 74% of all enrolled subjects, responded to the survey. Demographic data could be directly linked to response data using a subject identification number for 3359 of the 4042 respondents (Table 1). Although these data could not be linked for the other 683 respondents due to the lack of a subject identification number on the first 800 questionnaires distributed, the demographics of those with and without linkage data were nearly identical with respect to gender (chi-square analysis, $p=0.89$); age ($p=0.68$); race/ethnicity ($p=0.66$); family history ($p=0.99$); and findings at colonoscopy (polyps, $p=0.99$; cancer, $p=0.94$). Therefore, the survey data for the entire cohort of respondents ($n=4042$) are presented unless otherwise stated.

Patient Perceptions of Prep- and Test-Related Features

Overall, SB-DNA testing, FOBT, and colonoscopy received highly favorable mean ratings for each of the prep- and test-related features examined. As shown in Table 2, however, SB-DNA testing received higher mean ratings ($p<0.001$) than FOBT for simplicity of the stool sample collection process, comfort, perceived accuracy, and likelihood of repeating the test if recommended by their doctor. In contrast, FOBT received higher mean ratings ($p<0.01$) than SB-DNA testing for perceived prep-related anxiety. SB-DNA testing and FOBT received similar ratings for simplicity of bowel preparation instructions, perceived invasiveness, perceived embarrassment, and test-related anxiety. When compared with colonoscopy, both SB-DNA testing and FOBT received higher ratings ($p<0.001$) for all of the aforementioned prep- and test-related features, except accuracy, where colonoscopy was rated more favorably.

When asked about lost time from work or other activities, only 22.9% of respondents reported lost time due to the prep for colonoscopy and 34.1% due to the test itself, compared to <5% for SB-DNA testing and FOBT ($p<0.001$). The lower-than-expected percentages for colonoscopy presumably reflect the disproportionate number of subjects aged ≥65 years.

Patient Preferences

When asked explicitly which test was preferred for routine screening, 45% of respondents selected SB-DNA testing, 32% FOBT, and 15% colonoscopy ($p<0.001$); only 8% had no preference (Figure 1). Subgroup analyses were performed on the 3103 subjects expressing a preference for whom linkage data were available. The goal was to determine if patient preferences varied on the basis of age, gender, race/ethnicity, family history, or findings at colonoscopy. As shown in Table 3, SB-DNA testing was the preferred screening strategy by both men and women, subjects of all age groups, whites and nonwhites, and those with and without a family history of colorectal cancer. Patients found to have polyps at colonoscopy were significantly more likely to choose SB-DNA ($p<0.01$); in contrast, those found to have cancer were also more likely to prefer SB-DNA testing (40%) than FOBT (32%) or colonoscopy (28%), but differences did not achieve statistical significance ($p>0.05$), possibly because of the small number of subjects with cancer. All subgroups also preferred FOBT to colonoscopy, except patients found to have cancer.

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Table 2. Comparison of overall mean ratings[a] for SB DNA testing, FOBT, and colonoscopy (n=4042)

Question	SB-DNA (SD)	FOBT (SD)	Colonoscopy (SD)	Pairwise differences[b]
1. How easy or difficult to understand were the instructions about preparation for the test?	1.26 (0.56)	1.27 (0.57)	1.33 (0.67)	SB-DNA vs FOBT, NS SB-DNA vs CS, $p = 0.001$ FOBT vs CS, $p = 0.001$
2. How simple or complex was the stool sample collection process?	1.42 (0.71)	1.56 (0.82)	—	SB-DNA vs FOBT, $p < 0.001$
3. How easy or difficult was bowel purging for you?	—	—	2.26 (1.23)	
4. Overall, how comfortable or uncomfortable was the test?	1.39 (0.68)	1.45 (0.72)	1.90 (1.08)	SB-DNA vs FOBT, $p < 0.001$ SB-DNA vs CS, $p < 0.001$ FOBT vs CS, $p < 0.001$
5. How private or invasive did you consider the test to be?	1.26 (0.61)	1.27 (0.62)	2.13 (1.29)	SB-DNA vs FOBT, NS SB-DNA vs CS, $p < 0.001$ FOBT vs CS, $p < 0.001$
6. How embarrassing was it for you to take the test?	1.24 (0.62)	1.22 (0.58)	1.63 (1.00)	SB-DNA vs FOBT, NS SB-DNA vs CS, $p < 0.001$ FOBT vs CS, $p < 0.001$
7. Overall, how much anxiety or nervousness did preparation for the test cause you?	1.39 (0.75)	1.36 (0.72)	2.36 (1.24)	SB-DNA vs FOBT, $p < 0.01$ SB-DNA vs CS, $p < 0.001$ FOBT vs CS, $p < 0.001$
8. Overall, how much anxiety or nervousness did taking the test cause you?	1.33 (0.69)	1.31 (0.66)	2.23 (1.17)	SB-DNA vs FOBT, NS SB-DNA vs CS, $p < 0.001$ FOBT vs CS, $p < 0.001$
9. How accurate or inaccurate do you believe the test to be?	1.72 (0.84)	1.86 (0.93)	1.30 (0.72)	SB-DNA vs FOBT, $p < 0.001$ SB-DNA vs CS, $p < 0.001$ FOBT vs CS, $p < 0.001$
10. If your doctor recommended regular screening using the test, how likely or unlikely would you be to repeat it?	1.33 (0.76)	1.37 (0.80)	1.92 (1.23)	SB-DNA vs FOBT, $p < 0.001$ SB-DNA vs CS, $p < 0.001$ FOBT vs CS, $p < 0.001$

[a]Ratings expressed as mean (SD) using a five-point scale (1 = most favorable; 5 = least favorable).
[b]Bonferroni-adjusted p values for pairwise comparisons via signed-rank test.
CS, colonoscopy; FOBT, fecal occult blood testing; NS, not significant; SB-DNA, stool-based DNA testing; SD, standard deviation.

Discussion

This study found that many patients not only perceive stool-based DNA testing to be an acceptable alternative to both FOBT and colonoscopy, but also prefer stool-based DNA testing over both FOBT and colonoscopy for their routine CRC screening. Nearly half of all respondents selected stool-based DNA testing as their preferred screening strategy compared to about one third for FOBT and only 15% for colonoscopy. Interestingly, this preference for SB-DNA testing did not vary significantly on the basis of age, gender, race/ethnicity, family history, or findings at colonoscopy, with one notable exception: Individuals with colorectal cancers detected at colonoscopy were equally likely to choose any of the three screening modalities. These findings reinforce existing literature suggesting that patients have distinct preferences for screening.[16–18] These findings also suggest that many patients, including those at increased risk because of a positive family history or the presence of polyps or cancer at colonoscopy, prefer a convenient, noninvasive alternative to colonoscopy for their routine screening or surveillance. The extent to which patient knowledge, attitudes, or beliefs about personal susceptibility or disease severity influence these choices is unknown. Nevertheless, these findings have important implications with respect to adherence to serial screening or surveillance, especially since colonoscopy is advocated for those at increased risk by most authoritative groups.[3,4,6]

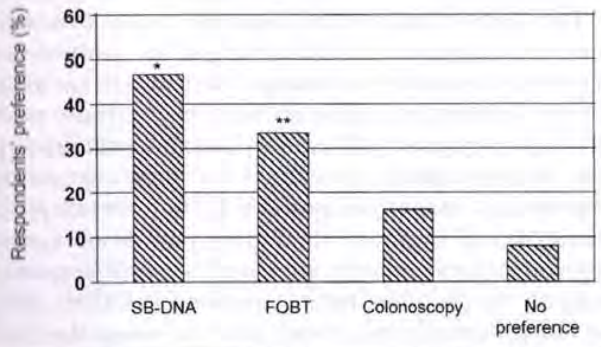


Figure 1. Preferred strategies for routine CRC screening (n =4042). FOBT, fecal occult blood testing; SB-DNA, stool-based DNA testing. *p <0.001, SB-DNA testing versus FOBT and colonoscopy. **p <0.001, FOBT versus colonoscopy.

Conceptually, stool-based DNA testing and FOBT share many similarities from the patient perspective. Both are safe, noninvasive stool-based tests with sample collection performed conveniently at home. Thus, the finding that most patients rated both tests comparably with respect to most prep- and test-related features is

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Table 3. Subgroup analyses of respondents expressing preferred strategy for routine colorectal cancer screening (n=3103)

Subgroup	n	Prefer SB-DNA (%)	Prefer FOBT (%)	Prefer colonoscopy (%)
Gender				
Female	1768	48.5[a]	33.9[b]	17.5
Male	1335	49.6[a]	36.5[b]	13.9
Age (years)				
50–54	155	59.1[a]	25.3[b]	15.6
55–64	459	53.8[a]	31.6[b]	14.6
≥65	2489	47.7[a]	36.7[b]	15.6
Race/ethnicity				
White	2785	49.9[a]	35.9[a]	14.1
Nonwhite	318	42.5[a]	30.5	27.0
Family history				
No	2667	49.0[a]	35.5[b]	15.5
Yes	436	49.8[a]	34.6[b]	15.6
Polyps detected[c]				
No	1651	49.8[a]	37.4[b]	12.8
Yes				
Cancer detected[c]				
No	3011	49.3[a]	35.4[b]	15.3
Yes	29	40.0	32.0	28.0

[a] $p \leq 0.01$ for SB-BNA vs FOBT and colonoscopy by chi-square goodness of fit.
[b] $p \leq 0.01$ for FOBT vs colonoscopy by chi-square goodness of fit.
[c] Data missing for 63 subjects (2.0%).
CS, colonoscopy; FOBT, fecal occult blood testing; SB-DNA, stool-based DNA testing.

not unexpected. Several noteworthy differences, however, were observed. Stool-based DNA testing received higher ratings for simplicity of the stool collection process and comfort, presumably attributable to the use of a specimen collection container that could be directly mounted onto the toilet seat, thus obviating the need for direct manipulation of stool as required for FOBT. Stool-based DNA testing was also perceived to have superior accuracy, possibly due to its more sophisticated, state-of-the-art technological basis. Importantly, stool-based DNA received more favorable ratings for likelihood of repeating the test if it was recommended by their physician. Conversely, FOBT received more favorable ratings for prep-related anxiety, which is curious since SB-DNA requires no specific preparation or dietary/medication restrictions. Despite their statistical significance, most of these differences were small, and therefore of questionable clinical significance. Nevertheless, extrapolation of these data would suggest that the perceived advantages of stool-based DNA testing supersede its relative disadvantages, thus accounting for the higher percentages of patients preferring stool-based DNA testing over FOBT for their routine screening.

Unlike FOBT and stool-based DNA testing, colonoscopy is a more complicated, risky, and invasive screening option, whose major advantages relate to its superior diagnostic accuracy and therapeutic capacity.[15,19,20] Previous studies have found that patients perceive colonoscopy to be more acceptable than both flexible sigmoidoscopy and double contrast barium.[21,22] This is the first study to directly compare patient perceptions of colonoscopy and stool-based screening tests. Not surprisingly, both stool-based DNA testing and FOBT received superior ratings to colonoscopy for all prep- and test-related features, except accuracy. Perhaps more importantly, both stool-based DNA testing and FOBT were preferred over colonoscopy for routine CRC screening. As previously noted, these findings validate the widespread belief that many patients prefer a convenient, noninvasive, albeit less-accurate screening alternative to colonoscopy for routine testing.

This study has several important strengths that lend credibility to its findings. Its large sample size involving patients from various clinical settings (academic centers, community hospitals, private practices) strengthens both external and internal validity. The high response rate, lack of prior screening experience other than possibly FOBT, and requirement that all respondents undergo all three screening modalities reduced the likelihood of response bias. Moreover, all subjects completed all three tests within a narrow time frame, thus reducing the likelihood of recall bias.

This study also has several important limitations. Its major limitation relates to the issue of patient acceptance. This study explores the perceptions and prefer-

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ences of patients based on their personal experiences with each of the screening tests. Only self-motivated patients willing to complete each of the three screening tests—that is, SB-DNA, FOBT, and colonoscopy—were eligible. Consequently, it remains unknown whether previously unscreened patients operating within an informed or shared decision-making model would express similar preferences if educated about the pros and cons of the various screening modalities based on input from their providers rather than personal experience. More importantly, it remains unknown whether patients who refuse other screening tests would perceive SB-DNA testing to be an acceptable alternative and adhere to a provider's recommendation to undergo screening.

The second major limitation relates to cost issues. Existing evidence clearly demonstrates that patient preferences for CRC screening tests are sensitive to out-of-pocket expenses.[17] Nevertheless, questions related to cost were excluded for two main reasons. First, at the time of survey, cost figures for SB-DNA testing were unavailable. Although perceived to be substantially more than FOBT, it was unclear how it would compare to colonoscopy. Second, it was speculated that SB-DNA testing, if deemed cost-effective, would ultimately be covered by many healthcare insurers, thus obviating concerns about cost. Although a recent economic analysis suggests that SB-DNA testing may be less cost-effective than the other currently recommended screening strategies,[23] improvements in sensitivity and heightened demand would have a favorable impact on cost-effectiveness.

The third limitation involves potential response bias related to the fact that the study was industry sponsored, and that subjects received compensation for their participation. The extent to which theses factors influenced subject responses is impossible to ascertain. Nevertheless, the large number of respondents, the fact that the survey was self-administered at home and returned by mail without subject identifiers other than subject numbers, and the disclaimer in the informed consent document that the sponsor was blinded to the response data help reduce concerns about the impact of this bias on results.

In conclusion, this study finds that many asymptomatic, average and moderate risk individuals not only perceive stool-based DNA testing to have a number of advantages over both FOBT and colonoscopy, but more importantly, prefer stool-based DNA testing to these other modalities for their routine CRC screening. These findings suggest that stool-based DNA testing may be an acceptable alternative to other currently recommended strategies and might increase participation rates. Future studies are needed to validate this speculation, and determine the extent to which stool-based DNA testing truly promotes patient acceptance and adherence to screening recommendations, particularly among individuals who might otherwise refuse screening.

What This Study Adds . . .

Poor patient acceptance is a major barrier to effective colorectal cancer screening.

Stool-based DNA (SB-DNA) testing is a novel screening strategy that offers a convenient, noninvasive, and potentially more acceptable alternative to existing screening tests.

This study is the first to assess and compare patient perceptions of stool-based DNA testing, fecal occult blood testing and colonoscopy.

We found that SB-DNA testing is not only acceptable but also preferred by many for routine screening.

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Abstract

Purpose

Colorectal cancer (CRC) is the second most deadly cancer in the USA. Early detection can improve CRC outcomes, but recent national screening rates (62%) remain below the 80% goal set by the National Colorectal Cancer Roundtable. Multiple options are endorsed for average-risk CRC screening, including the multi-target stool DNA (mt-sDNA) test. We evaluated cross-sectional mt-sDNA test completion in a population of commercially and Medicare-insured patients.

Methods

Participants included individuals ages 50 years and older with commercial insurance or Medicare, with a valid mt-sDNA test shipped by Exact Sciences Laboratories LLC between January 1, 2018, and December 31, 2018 (n = 1,420,460). In 2020, we analyzed cross-sectional adherence, as the percent of successfully completed tests within 365 days of shipment date.

Results

Overall cross-sectional adherence was 66.8%. Adherence was 72.1% in participants with Traditional Medicare, 69.1% in participants with Medicare Advantage, and 61.9% in participants with commercial insurance. Adherence increased with age: 60.8% for ages 50–64, 71.3% for ages 65–75, and 74.7% for ages 76 + years. Participants with mt-sDNA tests ordered by gastroenterologists had a higher adherence rate (78.3%) than those with orders by primary care clinicians (67.2%). Geographically, adherence rates were highest among highly rural patients (70.8%) and ordering providers in the Pacific region (71.4%).

Conclusions

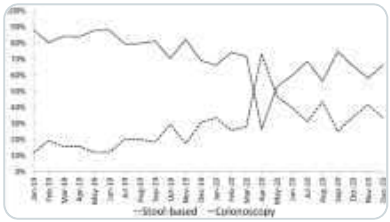
Data from this large, national sample of insured patients demonstrate high cross-sectional adherence with the mt-sDNA test, supporting its role as an accepted, noninvasive option for average-risk CRC screening. Attributes of mt-sDNA screening, including home-based convenience and accompanying navigation support, likely contributed to high completion rates.

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Introduction

Colorectal cancer (CRC) is the second leading cause of cancer deaths and fourth most diagnosed cancer in the USA [1], representing an ongoing public health concern, with estimates of 149,500 incident and 52,980 fatal cases in 2021 [2]. Average-risk CRC screening can favorably impact the CRC public health burden by identifying patients with premalignant or localized malignant neoplasia for earlier, more effective intervention. National organizations such as the United States Preventive Services Task Force (USPSTF) in their 2021 Final Recommendation Statement and the American Cancer Society (ACS) recommend lowering the age for average-risk CRC screening (beginning at the age of 45 years) using one of several equally endorsed test options, including the multi-target stool DNA assay [3,4,5] (mt-sDNA; marketed as Cologuard®; Exact Sciences, Madison, WI). Since receiving approval from the US Food and Drug Administration in August 2014, the mt-sDNA assay has been prescribed by over 200,000 providers and completed by more than 4 million patients nationwide.

Between 2015 and 2018, estimated CRC screening rates increased overall by 4.2%, from 61.7 to 65.9% according to National Health Interview Survey data [6, 7]. The same National Health Interview Survey (NHIS) data showed that for those who completed screening, 4.1% used mt-sDNA, and use was consistent across demographic subgroups such as sex, age, and race/ethnicity, with no apparent disparities. The number of people screened with the mt-sDNA test further increased in 2019, with 1.7 million patients successfully screened using mt-sDNA testing [8]. Despite the COVID-19 disruption, the at-home mt-sDNA test with its built-in navigation component for patients and providers and door-to-door shipping is uniquely positioned to sustain colorectal cancer screening efforts, potentially tempering the backlog of CRC screening delays and corresponding late-stage disease.

One critical component of effective CRC screening programs is patient adherence with completing the selected test option. The practical effectiveness of available screening strategies may be reduced by suboptimal adherence to screening recommendations [9]. Discouragingly, prior research has demonstrated relatively low completion rates for other stool-based CRC screening tests [9,10,11,12,13,14], and several recently conducted trials have revealed differences in CRC screening completion rates by test modality [9,10,11, 14]. These differences in completion rates may be exacerbated by multiple factors, such as socioeconomic status [15, 16] and race [17, 18]. Given the differences between endoscopic, radiologic, and stool-based screening strategies, accurate understanding of test-specific patient adherence is critical for population-, provider-, and payor-level discussions.

To date, analyses of mt-sDNA adherence have demonstrated high cross-sectional adherence rates (71%) but have been limited to Medicare beneficiaries to minimize the influence of insurance variability on test completion rates [19]. Given the growing adoption of mt-sDNA screening by commercial insurance plans, nearly all insured (> 94%) average-risk patients now have access to mt-sDNA screening with no out-of-pocket costs [20]. Thus, additional real-world assessment of mt-sDNA test adherence in non-Medicare patients is both feasible and timely. Here, we evaluated cross-sectional mt-sDNA test completion in a fully insured population and identified associated factors, to better inform shared decision-making, quality monitoring, and comparative effectiveness studies related to average-risk CRC screening.

Methods

Aggregate laboratory data from Exact Sciences Laboratories LLC (ESL; Madison, WI), the sole-source national laboratory for mt-sDNA testing, were retrospectively reviewed as part of ongoing laboratory quality management processes and in compliance with the Health Insurance Portability and Accountability Act. Per Mayo Clinic Institutional Review Board (IRB) criteria, this study was deemed as exempt from review.

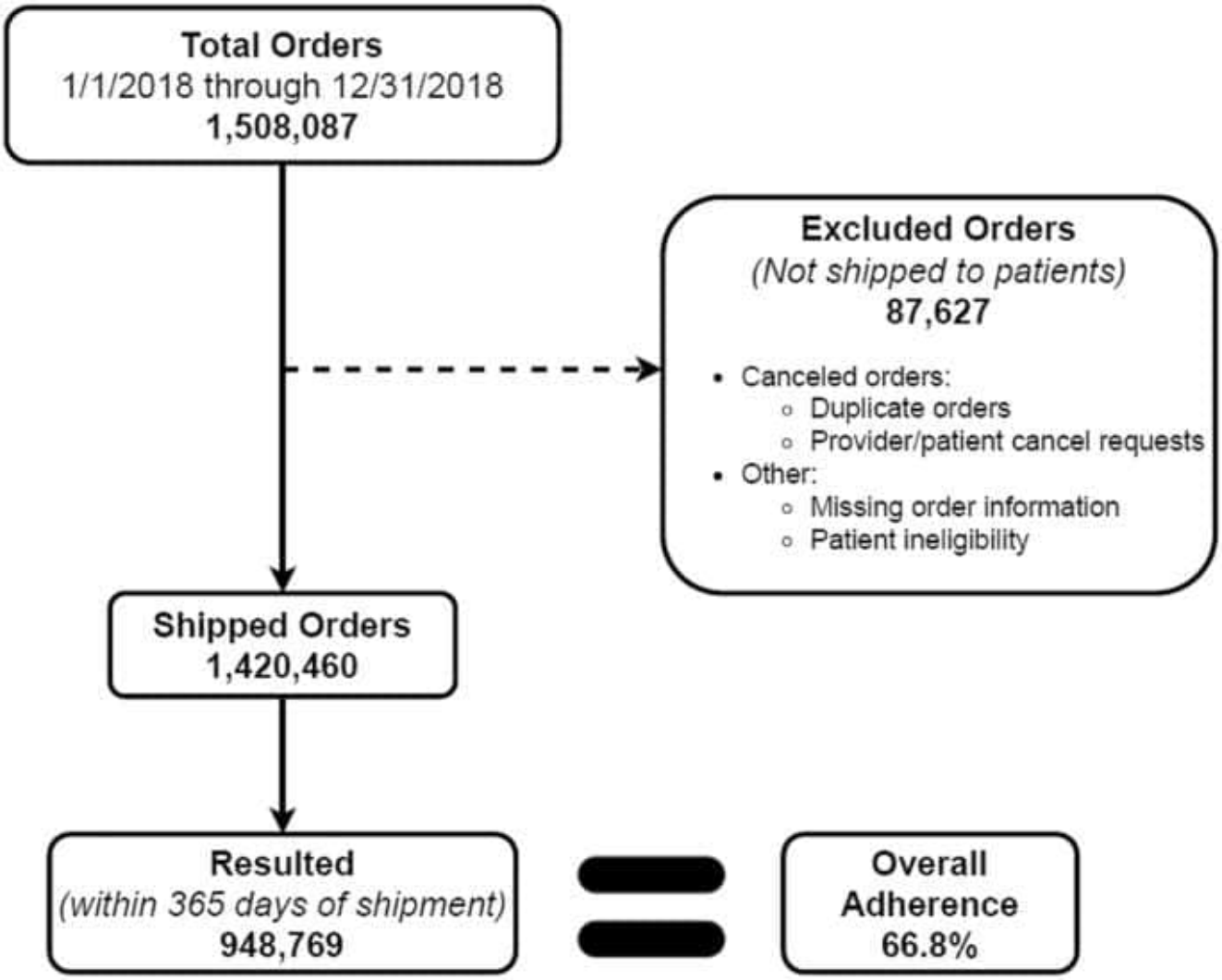
Study population, design, and data acquisition

Eligible study participants included individuals who met the following criteria: ages 50 years and older, covered by commercial insurance or Medicare, with a valid mt-sDNA test shipped to the order-specified address from ESL between January 1, 2018 and December 31, 2018. At the time of the study, the USPSTF recommendation was to start screening at 50 years old. Valid mt-sDNA test shipments were defined as having all information required for ESL to analyze the sample and report a positive or negative test result. Deidentified data referent to available patient (sex, age), provider (specialty, practice location), and test order features (testing status, time to completion) were sourced from the ESL internal data systems. Of note, patient race/ethnicity is listed as an optional field on the mt-sDNA order form and was additionally collected when available.

Information from ESL internal data systems regarding order characteristics was initially collected for 1,508,087 patients. Inclusion and exclusion criteria (including provider/patient cancellations, duplicate orders, missing information, and reasons for ineligibility) were utilized to comprise the final analysis cohort consisting of 1,420,460 patients. The cohort attrition flow chart outlines that cross-sectional adherence was defined as the percentage of eligible participants who successfully completed the test within 365 days of the shipment date (Fig. 1).

Fig. 1

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Study cohort—attrition flowchart

Sociodemographic characteristics including income and education are not tracked in the ESL test order data system. Therefore, these data were ascertained at the residential zip code level from public data sources, including the United States Census and American Community Surveys database [21,22,23].

Statistical analysis

Descriptive statistics were used to describe the baseline characteristics of the study population overall and by insurance type. Counts and percentages were used to describe population-level statistics while distribution statistics (mean and median) were provided, where appropriate, to further describe the study populations' time to adherence, overall

adherence, and age. Descriptive statistics were principally stratified by patient insurance type. Distribution statistics relating to skewness and other appropriate tests (e.g., chi-square test) were used as needed to describe the study population.

Given that the study population comprises the entirety of mt-sDNA patients during this time (N = 1,420,460), point estimates and p-value testing do not provide necessary context or support better comparison. In essence, very small differences, even if significant, are likely to arise due to the population size though do not reflect meaningful differences among populations. In contrast to significance tests, effect size is independent of sample size, while statistical significance can be dependent upon both sample size and effect size [24, 25]. To avoid confounding the meaning of significance due to such a large sample size, we decided not to report two-sided 95% confidence intervals for point estimates or two-sided p-values for subgroup comparisons.

Results

Of 1,420,460 patients who met the study criteria (Fig. 1), 61.2% were female with a mean age of 64.9 years. Age distributions were 50–64 years (47.3%), 65–75 years (40.0%), and 76 + years (12.7%), with the majority of the cohort residing in urban areas (70.4%). Of those who specified a race/ethnic category, the majority of participants were white, although most participants (85.6%) did not provide this optional information (Table 1). Within the study population, 46.1% had commercial insurance coverage, 33.5% had Traditional Medicare coverage, and 20.4% were covered by Medicare Advantage (Table 2). Patients residing in zip codes with above average Bachelor's degree attainment rates (35.0% of all adults above 25 in the USA had a Bachelor's degree as of 2018) [22] accounted for 31.2% of all shipments. Patients in zip codes with a median income greater than the national median ($33,706 per the American Community Survey conducted in 2018) [23] accounted for 43.3% of mt-sDNA test orders. Geographically, the highest adherence in the study population was observed for those dwelling in highly rural locations: urban (66.0%), rural (68.5%), and highly rural (70.8%) (Table 3). Most mt-sDNA test orders were placed by primary care clinicians (72.2%), followed by nurse practitioners and physician assistants (19.3%), gastroenterologists (3.2%), and obstetrics and gynecologists (1.8%), with the remaining mt-sDNA test orders placed by other specialties (3.5%) (Table 4).

Table 1 Study population demographics by insurance coverage type

Table 2 Cross-sectional adherence by patient factors

Table 3 Cross-sectional adherence by zip code population factors

Table 4 Cross-sectional adherence by provider-level factors

The overall cross-sectional adherence rate for the entire study population was 66.8% (948,769/1,420,460 patients received and completed the mt-sDNA test and had a valid result) with a median time-to-adherence (TTA) of 22 days. The difference in adherence between males and females was small (67.2 vs. 66.5%, respectively). Cross-sectional adherence was highest in patients with Traditional Medicare coverage (72.1%) and lowest in patients with commercial insurance coverage (61.9%). Adherence increased with age: 50–64 years (60.8%), 65–75 years (71.3%), and 76 + years (74.7%) overall, and within each of the insurance types (Table 2). Relative to those with commercial insurance, increases in adherence by age were more pronounced among those with Traditional Medicare or Medicare Advantage plans, who demonstrated lower rates of adherence among those 50–64 compared to those with commercial insurance (Table 2). Moreover, adherence was 73.6% for Traditional Medicare patients ages 65–75.

Statistically, cross-sectional adherence with the mt-sDNA test was not shown to be associated with level of education or median income of the zip code wherein patients resided.

Adherence was 66.0% in zip codes with an above average Bachelor's degree attainment rate compared with 67.2% in zip codes with a below average Bachelor's degree attainment rate. Similarly, adherence was 68.2% compared to 65.7% in zip codes with median incomes above and below the national median, respectively (Table 3).

Adherence also varied among ordering provider specialty and practice location. Patients with mt-sDNA tests ordered by gastroenterologists exhibited a higher adherence rate (78.3%) than those with orders placed by primary care clinicians (67.2%), nurse practitioners and physician assistants (63.5%), obstetricians and gynecologists (63.1%), and other specialties (67.3%). Adherence rates were highest among patients with ordering providers in the Pacific region (71.4%) and West North Central region (70.1%). Contrastingly, the lowest adherence was observed in the Mid-Atlantic region (65.7%), New England (65.2%), West South-Central region (64.6%), and Puerto Rico/US Territories (60.7%) (Table 4).

Discussion

Results from this retrospective study of a large, insured population demonstrate relatively high cross-sectional adherence with the mt-sDNA test for CRC screening. Adherence rates were similar between males and females and increased with age. Of note, area-level education and median income of patients' residential zip codes were not significantly associated with differences in adherence rates. Consistent with previous observations in Medicare patients [19], adherence rates were also higher for orders placed by gastroenterologists compared to other provider specialties. Geographically, the greatest adherence was observed among those living in highly rural areas; however, that population was only 3% of the overall cohort. Although GIs ordered the fewest mt-sDNA tests, the rate of adherence to recommendations by disease specialists may relate in part to more detailed discussion during encounters regarding the importance of completing CRC screening; albeit, this speculative interpretation requires further evaluation.

With nearly 1.5 million participants included in the study population, our data contributes to the emerging literature regarding mt-sDNA test adherence in the clinical setting, although in a younger and larger cohort than seen previously [19]. Overall adherence approached 67%, with meaningful differences observed between age groups. The highest rate was seen in the 76 + years subgroup having Traditional Medicare coverage. Adherence also increased

with age, from 60.8% in those 50–64 to 74.7% in patients ≥ 76 + years, while Traditional Medicare patients ages 65–75 exhibited 73.6% adherence.

The mt-sDNA test is offered in conjunction with patient and provider navigation support (available 24 h per day, 365 days per year, with translation services in over 240 languages). Previous studies have shown that patient navigation has a beneficial effect on patient health behavior, demonstrating increased CRC screening rates [19, 26, 27]. The amalgamation of test and navigation services was shown to be successful in a separate study of Medicare beneficiaries where individuals who were previously non-adherent with CRC screening were offered the mt-sDNA test, resulting in 88% completion and 96% diagnostic colonoscopy exam follow-up for those with a positive mt-sDNA result [28]. This intricate feature adds inherent value to the mt-sDNA test at no additional cost to the payor, health system, patient, or provider, while also improving the probability of test completion compared with no intervention [19,20,21,22,23,24,25,26,27,28,29]. This information may be helpful to consider as a guiding input variation for CRC modeling studies to investigate comparative effectiveness between screening modalities.

There is general agreement concerning the effectiveness of colorectal cancer screening; however, in contrast to other organ sites, major guideline groups have endorsed more than one test option for average-risk CRC screening in order to maximize engagement. Informed health care provider discussions and screening decisions are better guided by implementation considerations that can help patients select the testing option they are most likely to complete, and this factor is essential for reducing the number of CRC-related deaths in the USA. Prior research has demonstrated low completion rates for other CRC screening tests [9, 10], and existing literature on repeat screening with other non-mt-sDNA stool-based screening tests suggests a need for improvement [9,10,11, 30]. A more sensitive test, such as mt-sDNA, is less susceptible to drops in adherences rates. Mt-sDNA has a higher single application sensitivity for all stages of CRC, which distinguishes it from single marker fecal occult blood tests (FIT/gFOBT) [31]. The 10,000-person mt-sDNA pivotal study by Imperiale et al. [31] reported 92% sensitivity for CRC (vs 74% for FIT). This performance difference held true in receiver operating characteristic (ROC) analysis, regardless of the cutoff chosen for FIT. Higher one-time test sensitivity is relevant given that FIT adherence

to recommended screening frequency can drop off substantially after the first cycle of annual testing [32].

As an integral part of the screening process, the follow-up colonoscopy to a positive non-colonoscopy CRC screening exam is becoming increasingly appreciated in the literature. Follow-up colonoscopy after a positive first-line test is necessary for complete and effective CRC screening [33, 34]. Failure to, and delay of follow-up after a positive stool-based test has been associated with increased risk of later stage CRC and CRC mortality [33, 35,36,37]. Doubeni et al. found that patients failing to follow-up on abnormal FIT results face a sevenfold higher risk of dying of CRC than those who complete the follow-up process [37].

Differences have also been revealed in CRC screening completion rates by modality [13, 14]. In a study by Rutten et al. [14] among residents of Olmsted County, MN, eligible and due for CRC screening, it was revealed that CRC screening incidence rates remained stable from 2016 to 2018, while test-specific rates for mt-sDNA significantly increased. Moreover, the study revealed that adherence with follow-up colonoscopy within 6 months after a positive stool-based test was significantly higher among patients who underwent mt-sDNA screening versus FIT/FOBT (84.9% vs 42.6%, respectively). At real-world (imperfect) adherence rates of 40% for annual FIT and 70% for triennial mt-sDNA derived from a critical assessment of meta-analyses and retrospective cross-sectional data [19, 38] (in systems using FIT without a navigation program) [39], modeling illustrates that the number of LYG and reductions in CRC incidence and mortality were higher for triennial mt-sDNA [40].

Several geographic variations in adherence aligned with the currently reported US percentage of adults being up-to-date with CRC screening tests by state [41], with the highest rates seen in the Pacific and West North Central regions in our study, although adherence was lower in the New England and Middle Atlantic regions where up-to-date screening hovers around ≥ 70% and ≥ 65%, respectively.

Additionally, practice specialty was associated with higher cross-sectional adherence. Although gastroenterologists ordered fewer tests, adherence was lower among primary care providers. The observed difference in adherence by specialty could be related to various

provider factors (strength of screening recommendation, patient perception of specialty-related knowledge), patient factors (attitude concerning referral/follow-up completion), or a combination. It is also likely that patients who present to a gastroenterologist bring with them specific concerns which may serve as motivation to screen. Although test adherence rates differed by practice, recent literature has shown widespread awareness of the 2018 ACS CRC guidelines among primary care providers [42]. A 2020 survey study by the Montana Cancer Control Program revealed that fecal DNA testing has become much more popular since 2016, with more than a third (35.2%) of primary care providers reporting discussing it with patients in 2020 compared to only 4% in 2016 [43]. The same report from the Montana Department of Public Health and Human Services highlighted that in 2020 the fecal DNA test was the 3rd highest ranked CRC screening test prescribed with 86% of ordering providers considering the test effective. Future CRC screening studies can be tailored to garner information on provider ordering characteristics to better inform screening strategy, assess prescription differences, and develop provider education initiatives.

We would like to acknowledge several limitations of our study. First, there was limited reporting of ethnicity in this study population, with less than 15% of patients specifying a racial category. The unavailability of such data prohibited us from examining an important demographic aspect associated with screening adherence; thus, the differences observed among race/ethnicity were not overly considered due to a large percentage of participants not providing the optional information. Patient and provider factors analyzed in our study were limited to those characteristics that could be captured from the existing laboratory database. A more detailed assessment of factors suspected to influence mt-sDNA screening adherence, such as socioeconomic status along with a closer look at social determinants of health, will benefit future investigations. Secondly, we relied on determination of the mt-sDNA ordering clinician to define CRC average-risk status. Although indicated for mt-sDNA, we assumed that each provider appropriately followed test eligibility indications before prescribing, and we did not have access to sufficient data to confirm risk status for all participants in this real-world study. Thus, a percentage of off-label use can be logically assumed. Lastly, given the relative recency of mt-sDNA availability and adoption in clinical practice, we did not assess longitudinal adherence for the current study. Mt-sDNA test adherence was only evaluated on a cross-sectional basis with a review of associated patient

and provider factors over a 1-year study period. Further evaluation of longitudinal adherence with triennial mt-sDNA screening is anticipated in future studies.

Conclusions

Novel data from this large retrospective cohort of both Medicare and commercially insured patients revealed favorable adherence to CRC screening with the mt-sDNA assay test among eligible patients who met the study criteria, having a valid mt-sDNA test shipped to their order-specified address from ESL between January 1, 2018, and December 31, 2018. Innovative features of the mt-sDNA test such as the accompanying patient navigation system, together with its noninvasive approach and feasibility, likely impacted test completion rates. The highest adherence rates were observed among those covered by Medicare and for tests ordered by gastroenterologists. Our findings contribute valuable real-world data to the existing evidence base and provide clinical decision-makers with supportive information to recommend a guideline-endorsed CRC screening strategy, with the goal of increasing adherence through test completion. Future investigations examining longitudinal completion rates in accordance with national guidelines, as well as more detailed analyses of associations with socioeconomic, race/ethnicity, and other demographic factors on mt-sDNA test completion rates, are anticipated to complement this study.

Availability of data and materials

Study data are available upon reasonable request.

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Ethics declarations

Ethics approval

The data herein were retrospectively reviewed as part of ongoing laboratory (Exact Sciences Laboratories, LLC) quality management processes in compliance with the Health Insurance Portability and Accountability Act (HIPAA). The study was deemed exempt from IRB review by the Mayo Clinic Institutional Review Board.

Consent to participate/consent for publication

Not applicable; retrospective review of deidentified data.

Disclosure

LAMW, JVT, and BO are employees and shareholders of Exact Sciences. LJFR offers scientific input to research studies through a contracted services agreement between Mayo Clinic and Exact Sciences. PJL serves as Chief Medical Officer for Screening at Exact Sciences through a contracted services agreement with Mayo Clinic. PJL and Mayo Clinic have contractual rights to receive royalties through this agreement.

Conflict of interest

The authors declare no competing interests.

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ORIGINAL ARTICLE

Cross-sectional adherence with the multi-target stool DNA test for colorectal cancer screening in a large, nationally insured cohort

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Abstract

Purpose Colorectal cancer (CRC) is the second most deadly cancer in the USA. Early detection can improve CRC outcomes, but recent national screening rates (62%) remain below the 80% goal set by the National Colorectal Cancer Roundtable. Multiple options are endorsed for average-risk CRC screening, including the multi-target stool DNA (mt-sDNA) test. We evaluated cross-sectional mt-sDNA test completion in a population of commercially and Medicare-insured patients.

Methods Participants included individuals ages 50 years and older with commercial insurance or Medicare, with a valid mt-sDNA test shipped by Exact Sciences Laboratories LLC between January 1, 2018, and December 31, 2018 ($n = 1{,}420{,}460$). In 2020, we analyzed cross-sectional adherence, as the percent of successfully completed tests within 365 days of shipment date.

Results Overall cross-sectional adherence was 66.8%. Adherence was 72.1% in participants with Traditional Medicare, 69.1% in participants with Medicare Advantage, and 61.9% in participants with commercial insurance. Adherence increased with age: 60.8% for ages 50–64, 71.3% for ages 65–75, and 74.7% for ages 76 + years. Participants with mt-sDNA tests ordered by gastroenterologists had a higher adherence rate (78.3%) than those with orders by primary care clinicians (67.2%). Geographically, adherence rates were highest among highly rural patients (70.8%) and ordering providers in the Pacific region (71.4%).

Conclusions Data from this large, national sample of insured patients demonstrate high cross-sectional adherence with the mt-sDNA test, supporting its role as an accepted, noninvasive option for average-risk CRC screening. Attributes of mt-sDNA screening, including home-based convenience and accompanying navigation support, likely contributed to high completion rates.

Keywords Colorectal cancer screening/prevention · Colorectal neoplasms · Early detection of cancer · Mt-sDNA · Insurance

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer deaths and fourth most diagnosed cancer in the USA [1], representing an ongoing public health concern, with estimates of 149,500 incident and 52,980 fatal cases in 2021 [2]. Average-risk CRC screening can favorably impact the CRC public health burden by identifying patients with premalignant or localized malignant neoplasia for earlier, more effective intervention. National organizations such as the United States Preventive Services Task Force (USPSTF) in their 2021 Final Recommendation Statement and the American Cancer Society (ACS) recommend lowering the age for average-risk CRC screening (beginning at the age of 45 years) using one of several equally endorsed test options, including the multi-target stool DNA assay [3–5] (mt-sDNA; marketed as Cologuard®; Exact Sciences, Madison, WI). Since receiving approval from the US Food and Drug Administration in August 2014, the mt-sDNA assay has been prescribed by over 200,000 providers and completed by more than 4 million patients nationwide.

Between 2015 and 2018, estimated CRC screening rates increased overall by 4.2%, from 61.7 to 65.9% according to National Health Interview Survey data [6, 7]. The same National Health Interview Survey (NHIS) data showed that for those who completed screening, 4.1% used mt-sDNA, and use was consistent across demographic subgroups such as sex, age, and race/ethnicity, with no apparent

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disparities. The number of people screened with the mt-sDNA test further increased in 2019, with 1.7 million patients successfully screened using mt-sDNA testing [8]. Despite the COVID-19 disruption, the at-home mt-sDNA test with its built-in navigation component for patients and providers and door-to-door shipping is uniquely positioned to sustain colorectal cancer screening efforts, potentially tempering the backlog of CRC screening delays and corresponding late-stage disease.

One critical component of effective CRC screening programs is patient adherence with completing the selected test option. The practical effectiveness of available screening strategies may be reduced by suboptimal adherence to screening recommendations [9]. Discouragingly, prior research has demonstrated relatively low completion rates for other stool-based CRC screening tests [9–14], and several recently conducted trials have revealed differences in CRC screening completion rates by test modality [9–11, 14]. These differences in completion rates may be exacerbated by multiple factors, such as socioeconomic status [15, 16] and race [17, 18]. Given the differences between endoscopic, radiologic, and stool-based screening strategies, accurate understanding of test-specific patient adherence is critical for population-, provider-, and payor-level discussions.

To date, analyses of mt-sDNA adherence have demonstrated high cross-sectional adherence rates (71%) but have been limited to Medicare beneficiaries to minimize the influence of insurance variability on test completion rates [19]. Given the growing adoption of mt-sDNA screening by commercial insurance plans, nearly all insured (> 94%) average-risk patients now have access to mt-sDNA screening with no out-of-pocket costs [20]. Thus, additional real-world assessment of mt-sDNA test adherence in non-Medicare patients is both feasible and timely. Here, we evaluated cross-sectional mt-sDNA test completion in a fully insured population and identified associated factors, to better inform shared decision-making, quality monitoring, and comparative effectiveness studies related to average-risk CRC screening.

Methods

Aggregate laboratory data from Exact Sciences Laboratories LLC (ESL; Madison, WI), the sole-source national laboratory for mt-sDNA testing, were retrospectively reviewed as part of ongoing laboratory quality management processes and in compliance with the Health Insurance Portability and Accountability Act. Per Mayo Clinic Institutional Review Board (IRB) criteria, this study was deemed as exempt from review.

Study population, design, and data acquisition

Eligible study participants included individuals who met the following criteria: ages 50 years and older, covered by commercial insurance or Medicare, with a valid mt-sDNA test shipped to the order-specified address from ESL between January 1, 2018 and December 31, 2018. At the time of the study, the USPSTF recommendation was to start screening at 50 years old. Valid mt-sDNA test shipments were defined as having all information required for ESL to analyze the sample and report a positive or negative test result. Deidentified data referent to available patient (sex, age), provider (specialty, practice location), and test order features (testing status, time to completion) were sourced from the ESL internal data systems. Of note, patient race/ethnicity is listed as an optional field on the mt-sDNA order form and was additionally collected when available.

Information from ESL internal data systems regarding order characteristics was initially collected for 1,508,087 patients. Inclusion and exclusion criteria (including provider/patient cancellations, duplicate orders, missing information, and reasons for ineligibility) were utilized to comprise the final analysis cohort consisting of 1,420,460 patients. The cohort attrition flow chart outlines that cross-sectional adherence was defined as the percentage of eligible participants who successfully completed the test within 365 days of the shipment date (Fig. 1).

Sociodemographic characteristics including income and education are not tracked in the ESL test order data system. Therefore, these data were ascertained at the residential zip code level from public data sources, including the United States Census and American Community Surveys database [21–23].

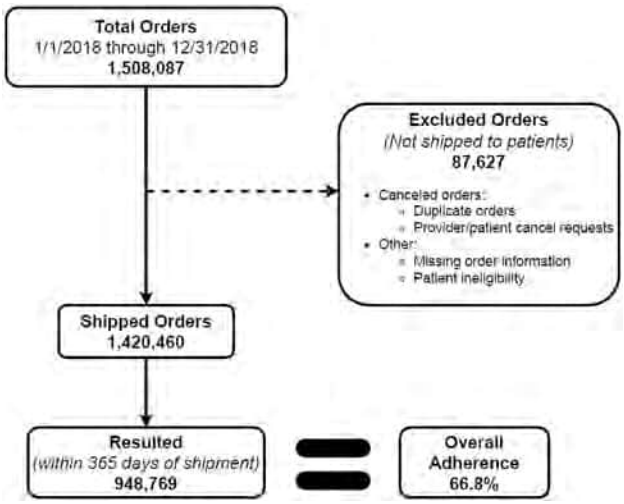


Fig. 1 Study cohort—attrition flowchart

Statistical analysis

Descriptive statistics were used to describe the baseline characteristics of the study population overall and by insurance type. Counts and percentages were used to describe population-level statistics while distribution statistics (mean and median) were provided, where appropriate, to further describe the study populations' time to adherence, overall adherence, and age. Descriptive statistics were principally stratified by patient insurance type. Distribution statistics relating to skewness and other appropriate tests (e.g., chi-square test) were used as needed to describe the study population.

Given that the study population comprises the entirety of mt-sDNA patients during this time ($N = 1{,}420{,}460$), point estimates and *p*-value testing do not provide necessary context or support better comparison. In essence, very small differences, even if significant, are likely to arise due to the population size though do not reflect meaningful differences among populations. In contrast to significance tests, effect size is independent of sample size, while statistical significance can be dependent upon both sample size and effect size [24, 25]. To avoid confounding the meaning of significance due to such a large sample size, we decided not to report two-sided 95% confidence intervals for point estimates or two-sided *p*-values for subgroup comparisons.

Results

Of 1,420,460 patients who met the study criteria (Fig. 1), 61.2% were female with a mean age of 64.9 years. Age distributions were 50–64 years (47.3%), 65–75 years (40.0%), and 76 + years (12.7%), with the majority of the cohort residing in urban areas (70.4%). Of those who specified a race/ethnic category, the majority of participants were white, although most participants (85.6%) did not provide this optional information (Table 1). Within the study population, 46.1% had commercial insurance coverage, 33.5% had Traditional Medicare coverage, and 20.4% were covered by Medicare Advantage (Table 2). Patients residing in zip codes with above average Bachelor's degree attainment rates (35.0% of all adults above 25 in the USA had a Bachelor's degree as of 2018) [22] accounted for 31.2% of all shipments. Patients in zip codes with a median income greater than the national median ($33,706 per the American Community Survey conducted in 2018) [23] accounted for 43.3% of mt-sDNA test orders. Geographically, the highest adherence in the study population was observed for those dwelling in highly rural locations: urban (66.0%), rural (68.5%), and highly rural (70.8%) (Table 3). Most mt-sDNA test orders were placed by primary care clinicians (72.2%), followed by nurse practitioners and physician assistants (19.3%), gastroenterologists (3.2%), and obstetrics and gynecologists

Table 1 Study population demographics by insurance coverage type

Category (% of cohort)	Insurance type			
	Commercial	Traditional Medicare	Medicare advantage	Total
Age				
50–64, *n* (%)	573,126 (87.5)	56,953 (12.0)	41,501 (14.3)	671,580 (47.3)
65–75, *n* (%)	71,187 (10.9)	307,007 (64.5)	190,617 (65.8)	568,811 (40.0)
76^{+}, *n* (%)	10,546 (1.6)	112,111 (23.5)	57,412 (19.8)	180,069 (12.7)
Totals	654,859	476,071	289,530	1,420,460
Sex				
Male, *n* (%)	260,436 (39.8)	178,860 (37.6)	110,708 (38.2)	550,004 (38.7)
Female, *n* (%)	394,174 (60.2)	296,962 (62.4)	178,732 (61.7)	869,868 (61.2)
Unspecified, *n* (%)	249 (0)	249 (0)	90 (0)	588 (0)
Race				
White (%)	87,625 (13.4)	60,967 (12.8)	35,393 (12.2)	183,985 (13.0)
Black or African American (%)	6999 (1.1)	4304 (0.9)	4298 (1.5)	15,601 (1.1)
American Indian/Alaska Native (%)	244 (0)	176 (0)	103 (0)	523 (0)
Asian (%)	2844 (0.4)	1034 (0.2)	820 (0.3)	4698 (0.3)
Native Hawaiian or other Pacific Islander (%)	190 (0)	119 (0)	79 (0)	388 (0)
Not specified (%)	556,957 (85.0)	409,471 (86.0)	248,837 (86.0)	1,215,265 (85.6)
Geography				
Urban (%)	471,962 (72.1)	317,426 (66.7)	210,140 (72.6)	999,528 (70.4)
Rural (%)	165,099 (25.2)	141,133 (29.6)	72,247 (25.0)	378,479 (26.7)
Highly rural (%)	17,798 (2.7)	17,512 (3.7)	7143 (2.5)	42,453 (3.0)

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Table 2 Cross-sectional adherence by patient factors

Patient-level factors	Cross-sectional adherence											
	Total			Commercial (46.1%)			Traditional Medicare (33.5%)			Medicare advantage (20.4%)		
	Completed/shipped	%	TTA	Completed/shipped	%	TTA	Completed/shipped	%	TTA	Completed/shipped	%	TTA
All eligible study patients	948,769/1,420,460	66.8	22	405,652/654,859	61.9	24	343,135/476,071	72.1	21	199,982/289,530	69.1	21
Age, years												
50–64	408,516/671,580	60.8	24	351,850/573,126	61.4	24	32,106/56,953	56.4	24	24,560/41,501	59.2	24
65–75	405,662/568,811	71.3	21	46,642/71,187	65.5	22	225,931/307,007	73.6	21	133,089/190,617	69.8	21
76^{+}	134,591/180,069	74.7	20	7160/10,546	67.9	20	85,098/112,111	75.9	20	42,333/57,412	73.7	20
Sex												
Male	369,655/550,004	67.2	21	162,896/260,436	62.5	23	129,790/178,860	72.6	20	76,969/110,708	69.5	20
Female	578,748/869,868	66.5	22	242,611/394,174	61.5	25	213,183/296,962	71.8	21	122,954/178,732	68.8	22
Not specified	366/588	62.2	26	145/249	58.2	27	162/249	65.1	27	59/90	65.6	21
Race												
White	118,016/183,985	64.1	23	52,668/87,625	60.1	25	42,056/60,967	69.0	22	23,292/35,393	65.8	22
Black or African American	7,972/15,601	51.1	24	3373/6999	48.2	26	2228/4304	51.8	23	2371/4298	55.2	23
American Indian/Alaska Native	290/523	55.4	24	145/244	59.4	24	88/176	50.0	23	57/103	55.3	23
Asian	2593/4698	55.2	23	1451/2844	51.0	24	667/1034	64.5	23	475/820	57.9	23
Native Hawaiian or other Pacific Islander	233/388	60.1	23	101/190	53.2	23	83/119	69.7	25	49/79	62.0	21
Not specified	819,665/1,215,265	67.4	22	347,914/556,957	62.5	24	298,013/409,471	72.8	21	173,738/248,837	69.8	21

TTA time to adherence (median days)

Table 3 Cross-sectional adherence by zip code population factors

Zip code population statistics	Cross-sectional adherence											
	Total			Commercial			Traditional Medicare			Medicare advantage		
	Completed/ordered	%	TTA	Completed/ordered	%	TTA	Completed/ordered	%	TTA	Completed/ordered	%	TTA
Employment status—unemployment rate												
Above national rate (70.9%)	667,427/1,006,915	66.3	21	276,955/451,104	61.4	22	241,674/337,704	71.6	21	148,798/218,107	68.2	21
Below national rate (29.1%)	281,342/413,545	68.0	22	128,697/203,755	63.2	23	101,461/138,367	73.3	21	51,184/71,423	71.7	22
Education level—bachelor's degree rate												
Above national rate (31.2%)	292,479/443,321	66.0	23	119,511/195,280	61.2	24	103,612/146,796	70.6	22	69,356/101,245	68.5	22
Below national rate (68.8%)	656,290/977,139	67.2	21	286,141/459,579	62.3	22	239,523/329,275	72.7	21	130,626/188,285	69.4	21
Median income												
Above national rate (43.3%)	419,161/614,364	68.2	22	192,521/303,687	63.4	24	147,879/199,270	74.2	22	78,761/111,407	70.7	22
Below national rate (56.7%)	529,608/806,096	65.7	22	213,131/351,172	60.7	22	195,256/276,801	70.5	21	121,221/178,123	68.1	21
Geography												
Urban (70.4%)	659,291/999,528	66.0	23	289,431/471,962	61.3	24	226,679/317,426	71.4	22	143,181/210,140	68.1	22
Rural (26.7%)	259,403/378,479	68.5	22	104,651/165,099	63.4	23	103,155/141,133	73.1	22	51,597/72,247	71.4	21
Highly rural (3.0%)	30,075/42,453	70.8	22	11,570/17,798	65.0	23	13,301/17,512	76.0	21	5204/7143	72.9	22

TTA time to adherence (median days)

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(1.8%), with the remaining mt-sDNA test orders placed by other specialties (3.5%) (Table 4).

The overall cross-sectional adherence rate for the entire study population was 66.8% (948,769/1,420,460 patients received and completed the mt-sDNA test and had a valid result) with a median time-to-adherence (TTA) of 22 days. The difference in adherence between males and females was small (67.2 vs. 66.5%, respectively). Cross-sectional adherence was highest in patients with Traditional Medicare coverage (72.1%) and lowest in patients with commercial insurance coverage (61.9%). Adherence increased with age: 50–64 years (60.8%), 65–75 years (71.3%), and 76 + years (74.7%) overall, and within each of the insurance types (Table 2). Relative to those with commercial insurance, increases in adherence by age were more pronounced among those with Traditional Medicare or Medicare Advantage plans, who demonstrated lower rates of adherence among those 50–64 compared to those with commercial insurance (Table 2). Moreover, adherence was 73.6% for Traditional Medicare patients ages 65–75.

Statistically, cross-sectional adherence with the mt-sDNA test was not shown to be associated with level of education or median income of the zip code wherein patients resided. Adherence was 66.0% in zip codes with an above average Bachelor's degree attainment rate compared with 67.2% in zip codes with a below average Bachelor's degree attainment rate. Similarly, adherence was 68.2% compared to 65.7% in zip codes with median incomes above and below the national median, respectively (Table 3).

Adherence also varied among ordering provider specialty and practice location. Patients with mt-sDNA tests ordered by gastroenterologists exhibited a higher adherence rate (78.3%) than those with orders placed by primary care clinicians (67.2%), nurse practitioners and physician assistants (63.5%), obstetricians and gynecologists (63.1%), and other specialties (67.3%). Adherence rates were highest among patients with ordering providers in the Pacific region (71.4%) and West North Central region (70.1%). Contrastingly, the lowest adherence was observed in the Mid-Atlantic region (65.7%), New England (65.2%), West South-Central region (64.6%), and Puerto Rico/US Territories (60.7%) (Table 4).

Discussion

Results from this retrospective study of a large, insured population demonstrate relatively high cross-sectional adherence with the mt-sDNA test for CRC screening. Adherence rates were similar between males and females and increased with age. Of note, area-level education and median income of patients' residential zip codes were not significantly associated with differences in adherence rates. Consistent with previous observations in Medicare patients [19], adherence rates were also higher for orders placed by gastroenterologists compared to other provider specialties. Geographically, the greatest adherence was observed among those living in highly rural areas; however, that population was only 3% of the overall cohort. Although GIs ordered the fewest mt-sDNA tests, the rate of adherence to recommendations by disease specialists may relate in part to more detailed discussion during encounters regarding the importance of completing CRC screening; albeit, this speculative interpretation requires further evaluation.

With nearly 1.5 million participants included in the study population, our data contributes to the emerging literature regarding mt-sDNA test adherence in the clinical setting, although in a younger and larger cohort than seen previously [19]. Overall adherence approached 67%, with meaningful differences observed between age groups. The highest rate was seen in the 76 + years subgroup having Traditional Medicare coverage. Adherence also increased with age, from 60.8% in those 50–64 to 74.7% in patients ≥ 76 + years, while Traditional Medicare patients ages 65–75 exhibited 73.6% adherence.

The mt-sDNA test is offered in conjunction with patient and provider navigation support (available 24 h per day, 365 days per year, with translation services in over 240 languages). Previous studies have shown that patient navigation has a beneficial effect on patient health behavior, demonstrating increased CRC screening rates [19, 26, 27]. The amalgamation of test and navigation services was shown to be successful in a separate study of Medicare beneficiaries where individuals who were previously non-adherent with CRC screening were offered the mt-sDNA test, resulting in 88% completion and 96% diagnostic colonoscopy exam follow-up for those with a positive mt-sDNA result [28]. This intricate feature adds inherent value to the mt-sDNA test at no additional cost to the payor, health system, patient, or provider, while also improving the probability of test completion compared with no intervention [19–29]. This information may be helpful to consider as a guiding input variation for CRC modeling studies to investigate comparative effectiveness between screening modalities.

There is general agreement concerning the effectiveness of colorectal cancer screening; however, in contrast to other organ sites, major guideline groups have endorsed more than one test option for average-risk CRC screening in order to maximize engagement. Informed health care provider discussions and screening decisions are better guided by implementation considerations that can help patients select the testing option they are most likely to complete, and this factor is essential for reducing the number of CRC-related deaths in the USA. Prior research has demonstrated low completion rates for other CRC screening tests [9, 10], and existing literature on repeat screening with other non-mt-sDNA

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Table 4 Cross-sectional adherence by provider-level factors

Provider-level factors	Cross-sectional adherence											
	Total			Commercial			Traditional Medicare			Medicare advantage		
	Completed/ordered	%	TTA	Completed/ordered	%	TTA	Completed/ordered	%	TTA	Completed/ordered	%	TTA
Specialty												
GI (3.2%)	35,381/45,204	78.3	20	8,830/12,106	72.9	22	19,296/23,920	80.7	20	7255/9178	79	20
OB/GYN (1.8%)	16,149/25,597	63.1	24	10,817/17,220	62.8	26	3660/4855	75.4	22	1672/3522	47.5	23
Primary care (72.2%)	689,393/1,025,331	67.2	22	288,894/462,109	62.5	24	249,634/345,462	72.3	21	150,865/217,760	69.3	21
NP/PA (19.3%)	174,441/274,694	63.5	22	83,070/141,027	58.9	24	57,167/83,264	68.7	21	34,204/50,403	67.9	21
Other (3.5%)	33,405/49,634	67.3	22	14,041/22,397	62.7	24	13,378/18,570	72	21	5986/8667	69.1	21
Practice location (region)												
East North Central	200,228/301,581	66.4	21	93,746/151,818	61.7	23	63,003/89,215	70.6	20	43,479/60,548	71.8	20
East South Central	67,801/101,257	67	20	25,800/41,222	62.6	22	24,040/33,879	71	19	17,961/26,156	68.7	20
Mid-Atlantic	112,383/171,083	65.7	23	49,104/79,746	61.6	25	38,759/55,519	69.8	21	24,520/35,818	68.5	22
Mountain	63,508/95,063	66.8	23	23,060/36,321	63.5	26	23,203/30,882	75.1	22	17,245/27,860	61.9	23
New England	44,068/67,562	65.2	24	21,710/35,799	60.6	27	14,606/20,885	69.9	22	7752/10,878	71.3	23
Pacific	56,805/79,522	71.4	25	23,117/34/519	67	27	26,858/35,750	75.1	23	6830/9253	73.8	24
South Atlantic	229,657/342,664	67	21	93,501/152,993	61.1	23	89,721/123,081	72.9	20	46,435/66,590	69.7	21
West North Central	67,400/96,140	70.1	22	30,671/46,937	65.3	23	25,984/34,687	74.9	20	10,745/14,516	74	21
West South Central	106,707/165,239	64.6	22	44,860/75,362	59.5	24	36,878/52,044	70.9	21	24,969/37,833	66	22
Puerto Rico and US Territories	212/349	60.7	24	83/142	58.5	25	83/129	64.3	24	46/78	59	23

GI gastroenterology, *GYN* gynecology, *NP* nurse practitioner, *OB* obstetrics, *PA* physician assistant, *TTA* time to adherence (median days)

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stool-based screening tests suggests a need for improvement [9–11, 30]. A more sensitive test, such as mt-sDNA, is less susceptible to drops in adherences rates. Mt-sDNA has a higher single application sensitivity for all stages of CRC, which distinguishes it from single marker fecal occult blood tests (FIT/gFOBT) [31]. The 10,000-person mt-sDNA pivotal study by Imperiale et al. [31] reported 92% sensitivity for CRC (vs 74% for FIT). This performance difference held true in receiver operating characteristic (ROC) analysis, regardless of the cutoff chosen for FIT. Higher one-time test sensitivity is relevant given that FIT adherence to recommended screening frequency can drop off substantially after the first cycle of annual testing [32].

As an integral part of the screening process, the follow-up colonoscopy to a positive non-colonoscopy CRC screening exam is becoming increasingly appreciated in the literature. Follow-up colonoscopy after a positive first-line test is necessary for complete and effective CRC screening [33, 34]. Failure to, and delay of follow-up after a positive stool-based test has been associated with increased risk of later stage CRC and CRC mortality [33, 35–37]. Doubeni et al. found that patients failing to follow-up on abnormal FIT results face a sevenfold higher risk of dying of CRC than those who complete the follow-up process [37].

Differences have also been revealed in CRC screening completion rates by modality [13, 14]. In a study by Rutten et al. [14] among residents of Olmsted County, MN, eligible and due for CRC screening, it was revealed that CRC screening incidence rates remained stable from 2016 to 2018, while test-specific rates for mt-sDNA significantly increased. Moreover, the study revealed that adherence with follow-up colonoscopy within 6 months after a positive stool-based test was significantly higher among patients who underwent mt-sDNA screening versus FIT/FOBT (84.9% vs 42.6%, respectively). At real-world (imperfect) adherence rates of 40% for annual FIT and 70% for triennial mt-sDNA derived from a critical assessment of meta-analyses and retrospective cross-sectional data [19, 38] (in systems using FIT without a navigation program) [39], modeling illustrates that the number of LYG and reductions in CRC incidence and mortality were higher for triennial mt-sDNA [40].

Several geographic variations in adherence aligned with the currently reported US percentage of adults being up-to-date with CRC screening tests by state [41], with the highest rates seen in the Pacific and West North Central regions in our study, although adherence was lower in the New England and Middle Atlantic regions where up-to-date screening hovers around $\geq 70\%$ and $\geq 65\%$, respectively.

Additionally, practice specialty was associated with higher cross-sectional adherence. Although gastroenterologists ordered fewer tests, adherence was lower among primary care providers. The observed difference in adherence by specialty could be related to various provider factors (strength of screening recommendation, patient perception of specialty-related knowledge), patient factors (attitude concerning referral/follow-up completion), or a combination. It is also likely that patients who present to a gastroenterologist bring with them specific concerns which may serve as motivation to screen. Although test adherence rates differed by practice, recent literature has shown widespread awareness of the 2018 ACS CRC guidelines among primary care providers [42]. A 2020 survey study by the Montana Cancer Control Program revealed that fecal DNA testing has become much more popular since 2016, with more than a third (35.2%) of primary care providers reporting discussing it with patients in 2020 compared to only 4% in 2016 [43]. The same report from the Montana Department of Public Health and Human Services highlighted that in 2020 the fecal DNA test was the 3rd highest ranked CRC screening test prescribed with 86% of ordering providers considering the test effective. Future CRC screening studies can be tailored to garner information on provider ordering characteristics to better inform screening strategy, assess prescription differences, and develop provider education initiatives.

We would like to acknowledge several limitations of our study. First, there was limited reporting of ethnicity in this study population, with less than 15% of patients specifying a racial category. The unavailability of such data prohibited us from examining an important demographic aspect associated with screening adherence; thus, the differences observed among race/ethnicity were not overly considered due to a large percentage of participants not providing the optional information. Patient and provider factors analyzed in our study were limited to those characteristics that could be captured from the existing laboratory database. A more detailed assessment of factors suspected to influence mt-sDNA screening adherence, such as socioeconomic status along with a closer look at social determinants of health, will benefit future investigations. Secondly, we relied on determination of the mt-sDNA ordering clinician to define CRC average-risk status. Although indicated for mt-sDNA, we assumed that each provider appropriately followed test eligibility indications before prescribing, and we did not have access to sufficient data to confirm risk status for all participants in this real-world study. Thus, a percentage of off-label use can be logically assumed. Lastly, given the relative recency of mt-sDNA availability and adoption in clinical practice, we did not assess longitudinal adherence for the current study. Mt-sDNA test adherence was only evaluated on a cross-sectional basis with a review of associated patient and provider factors over a 1-year study period. Further evaluation of longitudinal adherence with triennial mt-sDNA screening is anticipated in future studies.

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Conclusions

Novel data from this large retrospective cohort of both Medicare and commercially insured patients revealed favorable adherence to CRC screening with the mt-sDNA assay test among eligible patients who met the study criteria, having a valid mt-sDNA test shipped to their order-specified address from ESL between January 1, 2018, and December 31, 2018. Innovative features of the mt-sDNA test such as the accompanying patient navigation system, together with its noninvasive approach and feasibility, likely impacted test completion rates. The highest adherence rates were observed among those covered by Medicare and for tests ordered by gastroenterologists. Our findings contribute valuable real-world data to the existing evidence base and provide clinical decision-makers with supportive information to recommend a guideline-endorsed CRC screening strategy, with the goal of increasing adherence through test completion. Future investigations examining longitudinal completion rates in accordance with national guidelines, as well as more detailed analyses of associations with socioeconomic, race/ethnicity, and other demographic factors on mt-sDNA test completion rates, are anticipated to complement this study.

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Author contribution Conceptualization—Lesley-Ann Miller-Wilson, Lila J Finney Rutten, Paul J Limburg, Ahmet Burak Ozbay. Data curation—Jack Van Thomme. Formal analysis—all authors. Investigation—Lesley-Ann Miller-Wilson, Jack Van Thomme. Methodology—all authors. Project administration—Lesley-Ann Miller-Wilson, Jack Van Thomme. Resources—Lesley-Ann Miller-Wilson, Jack Van Thomme, Paul J Limburg. Software—Jack Van Thomme. Supervision—Lesley-Ann Miller-Wilson, Paul J Limburg. Validation—Lesley-Ann Miller-Wilson, Jack Van Thomme. Visualization—Lesley-Ann Miller-Wilson, Jack Van Thomme. Writing (original draft)—all authors. Writing (review & editing)—all authors.

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Availability of data and materials Study data are available upon reasonable request.

Declarations

Ethics approval The data herein were retrospectively reviewed as part of ongoing laboratory (Exact Sciences Laboratories, LLC) quality management processes in compliance with the Health Insurance Portability and Accountability Act (HIPAA). The study was deemed exempt from IRB review by the Mayo Clinic Institutional Review Board.

Consent to participate/consent for publication Not applicable; retrospective review of deidentified data.

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Conflict of interest The authors declare no competing interests.

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040			a| NSD b| eng c| NSD d| MXC d| OCLCQ d| MUQ d| OCLCQ d| OCL d| SBH d| OCLCQ d| LGG d| FFQ d| OCLCQ d| OCLCE d| CCT d| OCLCQ d| OPELS d| DLC d| OCLCF d| OCLCO d| CUD d| VT2 d| OCLCQ d| OCLCO d| OCLCQ d| OCLCO d| OCLCQ d| OCLCA d| BUF d| U3W d| EZC d| FQM d| UKMGB d| OCLCO d| OCLCQ d| WYU d| OCLCO d| OCL d| OCLCQ d| WaSeSS	
042			a| nsdp a| pcc a| dlr	
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130	0		a| Gastroenterology (Online)	
210	0		a| Gastroenterology b| (Online)	
222		0	a| Gastroenterology b| (Online)	
245	1	0	a| Gastroenterology h| [electronic resource] : b| official journal of the American Gastroenterologic Association.	
260			a| [Philadelphia, Pa.] : b| W.B. Saunders	
310			a| Monthly	
362	1		a| Print began with vol. 1 (Jan. 1943).	
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650		0	a| Gastroenterology v| Periodicals.	
650		0	a| Gastrointestinal system x| Diseases.	
650		2	a| Gastrointestinal Diseases	
655		2	a| Periodical	
710	2		a| American Gastroenterologic Association.	
776	0	8	i| Print version: t| Gastroenterology x| 0016-5085 w| (DLC)med47002225 w| (OCoLC)1570457	
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Gastroenterology [electronic resource] : official journal of the American Gastroenterologic Association

Uniform Title	Gastroenterology (Online)
Additional Titles	Gastroenterology (Online)
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