INVITAE

INVITAE DIAGNOSTIC TESTING RESULTS

Patient name:	John R Zoubek	**Sample type:**	Saliva	**Report date:**	18-AUG-2023
DOB:	20-DEC-1979	**Sample collection date:**	23-FEB-2021	**Invitae #:**	RQ2026347-1
Sex assigned at birth:	Male	**Sample accession date:**	27-FEB-2021	**Clinical team:**	GC HIS Lisa Schimmenti
Gender:					
Patient ID (MRN):	12-097-059				

Reason for testing

Diagnostic test for a personal history of disease

Test performed

Sequence analysis and deletion/duplication testing of the 407 genes listed in the Genes Analyzed section.

- Invitae Primary Immunodeficiency Panel

ADDENDED REPORT

This report supersedes RQ2026347 (25-MAR-2021) and updates the interpretation of the variant(s) in the table below.

- The change in variant classification was made as a result of re-review of the evidence in light of new variant interpretation guidelines and/or new information. Updating variant classification may result in variant(s) being added to, removed from, or moved to a different section of the report.

Updated Interpretations

GENE	VARIANT	ZYGOSITY	PRIOR VARIANT CLASSIFICATION	NEW VARIANT CLASSIFICATION
ATM	c.2922-50_2940del (Splice site)	heterozygous	Likely Pathogenic	PATHOGENIC

RESULT: POSITIVE

One Pathogenic variant identified in ATM. ATM is associated with autosomal dominant predisposition to certain cancers and autosomal recessive ataxia-telangiectasia.

Additional Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
ATM	c.2922-50_2940del (Splice site)	heterozygous	PATHOGENIC
ICOSLG	c.866C>T (p.Ala289Val)	heterozygous	Uncertain Significance

About this test

This diagnostic test evaluates 407 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

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Next steps

- This is a medically important result that should be discussed with a healthcare provider, such as a genetic counselor, to learn more about this result and the appropriate next steps for further evaluation, treatment and/or management. This result should be interpreted within the context of additional laboratory results, family history and clinical findings.
- Please see NCCN (**www.nccn.org**), PMID: 34234451, 28318010, 28572264, 35454905, and 28225426 for management guidelines regarding ATM-related condition(s).
- Consider sharing this result with relatives as they may also be at risk. Details on our Family Variant Testing program can be found at **www.invitae.com/family**.
- Register your test at **www.invitae.com/patients** to download a digital copy of your results. You can also access educational resources about how your results can help inform your health.

Clinical summary

A Pathogenic variant, c.2922-50_2940del (Splice site), was identified in ATM.

- The ATM gene is associated with autosomal dominant predisposition to breast, ovarian, pancreatic (PMID: 26483394, 28888541, 30733081), and prostate cancer (PMID: 27989354, 28657667). ATM is also associated with autosomal recessive ataxia-telangiectasia (A-T) (MedGen UID: 439). Additionally, the ATM gene has preliminary evidence supporting a correlation with autosomal dominant predisposition to gastric (PMID: 26182300) and colon cancer (PMID: 30862463).
- This result is consistent with a predisposition to, or diagnosis of, autosomal dominant ATM-related conditions.
- The lifetime risk of breast cancer in females with one pathogenic ATM variant is approximately 21-33% (PMID: 30733081, 33471974, 27112364). There is also an increased risk of ovarian, pancreatic, and prostate cancer; however, lifetime risks are not established (PMID: 30733081, 28767289, 27989354).

  Classic A-T is characterized by progressive cerebellar ataxia beginning in early childhood with symptoms including oculomotor apraxia, choreoathetosis, telangiectasias of the conjunctivae, immunodeficiency, frequent infections, and increased malignancy risk, particularly for leukemia and lymphoma (PMID: 15279807, 26050521). Variant A-T is similar to classic A-T in terms of symptoms and increased malignancy risk, but severity tends to be milder and have a later age of onset.

  It should be noted that acquired (somatic) variants may arise in the blood, particularly with advancing age, and may even appear heterozygous (PMID: 25426837, 25426838, 33864022). Results using specimens containing leukocytes may not distinguish between germline and acquired variants and additional testing may be appropriate.
- Biological relatives have a chance of being at risk for autosomal dominant ATM-related conditions and have a chance of being carriers for autosomal recessive ATM-related conditions. Those at risk should consider testing.

A Variant of Uncertain Significance, c.866C>T (p.Ala289Val), was identified in ICOSLG.

- The ICOSLG gene currently has no well-established disease association; however, there is preliminary evidence supporting a correlation with autosomal recessive combined immunodeficiency (PMID: 30498080).
- Not all variants present in a gene cause disease. The clinical significance of the variant(s) identified in this gene is uncertain. Until this uncertainty can be resolved, caution should be exercised before using this result to inform clinical management decisions.
- Familial VUS testing is not offered. Testing family members for this variant will not contribute evidence to allow variant reclassification. Details on our VUS Resolution and Family Variant Testing Programs can be found at https://www.invitae.com/family.

Variant details

ATM, Exon 20, c.2922-50_2940del (Splice site), heterozygous, PATHOGENIC

- This variant results in the deletion of part of exon 20 (c.2922-50_2940del) of the ATM gene. RNA analysis indicates that this variant induces altered splicing and may result in an absent or disrupted protein product.
- This variant is not present in population databases (gnomAD no frequency).
- This variant has not been reported in the literature in individuals affected with ATM-related conditions.
- ClinVar contains an entry for this variant (Variation ID: 407642).
- Studies have shown that this variant results in activation of a cryptic splice site and introduces a premature termination codon (Invitae). The resulting mRNA is expected to undergo nonsense-mediated decay.
- This variant disrupts a region of the ATM protein in which other variant(s) (p.Cys977Tyr) have been determined to be pathogenic (PMID: 34445196; Invitae). This suggests that this is a clinically significant region of the protein, and that variants that disrupt it are likely to be disease-causing.
- For these reasons, this variant has been classified as Pathogenic.

ICOSLG, Exon 6, c.866C>T (p.Ala289Val), heterozygous, Uncertain Significance

- This sequence change replaces alanine, which is neutral and non-polar, with valine, which is neutral and non-polar, at codon 289 of the ICOSLG protein (p.Ala289Val).
- This variant is present in population databases (rs199878735, gnomAD 0.07%), and has an allele count higher than expected for a pathogenic variant.
- This variant has not been reported in the literature in individuals affected with ICOSLG-related conditions.
- ClinVar contains an entry for this variant (Variation ID: 1372557).
- Algorithms developed to predict the effect of missense changes on protein structure and function output the following: SIFT: "Not Available"; PolyPhen-2: "Benign"; Align-GVGD: "Not Available". The valine amino acid residue is found in multiple mammalian species, which suggests that this missense change does not adversely affect protein function.
- In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.

Genes analyzed

This table represents a complete list of genes analyzed for this individual, including the relevant gene transcript(s). If more than one transcript is listed for a single gene, variants were reported using the first transcript listed unless otherwise indicated in the report. An asterisk (*) indicates that this gene has a limitation. Please see the Limitations section for details. Results are negative unless otherwise indicated in the report. Benign and Likely Benign variants are not included in this report and in specific scenarios variants of uncertain significance in the requisitioned gene(s) may not be included in this report. These variants are available upon request.

GENE	TRANSCRIPT
ACD	NM_001082486.1
ACP5	NM_001111035.2
ACTB	NM_001101.3
ADA	NM_000022.2
ADA2	NM_001282225.1
ADAM17	NM_003183.5
ADAR	NM_001111.4
AICDA	NM_020661.2
AIRE	NM_000383.3
AK2	NM_001625.3
ALG6	NM_013339.3
ANGPT1	NM_001146.4
ANKZF1	NM_018089.2
AP3B1	NM_003664.4
AP3D1	NM_001261826.1
ARHGEF1	NM_199002.1
ARPC1B	NM_005720.3
ASAH1	NM_177924.3
ATM*	NM_000051.3
ATP6AP1	NM_001183.5
B2M	NM_004048.2
BACH2	NM_021813.3
BCL10	NM_003921.4
BCL11B	NM_138576.3
BLM	NM_000057.3
BLNK	NM_013314.3
BLOC1S3	NM_212550.4
BLOC1S6	NM_012388.3
BTK	NM_000061.2
C17orf62	NM_001033046.3
C1QA	NM_015991.2
C1QB	NM_000491.3
C1QC	NM_172369.3
C1S	NM_201442.2
C2	NM_000063.5
C3	NM_000064.3
C5	NM_001735.2
C6	NM_000065.3
C7	NM_000587.2
C8A	NM_000562.2
C8B	NM_000066.3
C9	NM_001737.4
CARD11	NM_032415.5
CARD14	NM_024110.4
CARD8	NM_014959.3
CARD9	NM_052813.4
CARMIL2	NM_001013838.1
CASP10	NM_032977.3
CASP8	NM_001228.4
CBL	NM_005188.3
CCBE1	NM_133459.3
CD19	NM_001770.5
CD247	NM_198053.2
CD27	NM_001242.4
CD3D	NM_000732.4
CD3E	NM_000733.3
CD3G	NM_000073.2
CD40	NM_001250.5
CD40LG	NM_000074.2
CD46	NM_002389.4
CD55	NM_000574.4
CD59	NM_203330.2
CD79A	NM_001783.3
CD79B	NM_000626.3
CD81	NM_004356.3
CD8A	NM_001768.6
CDC42	NM_001791.3
CDCA7	NM_031942.4
CEBPE	NM_001805.3
CFB	NM_001710.5
CFD	NM_001928.3
CFH*	NM_000186.3
CFI	NM_000204.4
CFP	NM_002621.2
CHD7	NM_017780.3
CIB1	NM_001277764.1
CIITA	NM_000246.3
CLCN7	NM_001287.5
CLPB	NM_030813.5
COL7A1	NM_000094.3
COPA	NM_004371.3
CORO1A*	NM_007074.3
CR2	NM_001006658.2
CSF2RA*	NM_006140.4
CSF2RB	NM_000395.2
CSF3R	NM_000760.3
CTC1	NM_025099.5
CTLA4	NM_005214.4
CTPS1	NM_001905.3
CTSC	NM_001814.5
CXCR2	NM_001557.3
CXCR4	NM_003467.2
CYBA	NM_000101.3
CYBB	NM_000397.3
CYP27A1	NM_000784.3
DCLRE1C	NM_001033855.2
DDX58	NM_014314.3
DEF6	NM_022047.3
DGAT1	NM_012079.5
DIAPH1	NM_005219.4
DKC1	NM_001363.4
DNAJC21	NM_001012339.2

GENE	TRANSCRIPT
DNASE1L3	NM_004944.3
DNASE2	NM_001375.2
DNMT3B	NM_006892.3
DOCK2	NM_004946.2
DOCK8	NM_203447.3
DSG1	NM_001942.3
DTNBP1	NM_032122.4
DUOX2*	NM_014080.4
EFL1*	NM_024580.5
EIF2AK3	NM_004836.6
ELANE	NM_001972.2
EPG5	NM_020964.2
ERBIN	NM_001253697.1
ERCC2	NM_000400.3
ERCC3	NM_000122.1
ERCC6L2	NM_020207.4
EXTL3	NM_001440.3
FADD	NM_003824.3
FANCA	NM_000135.2
FANCB	NM_001018113.1
FANCE	NM_021922.2
FANCF	NM_022725.3
FANCI	NM_001113378.1
FANCL*	NM_018062.3
FAS	NM_000043.5
FASLG	NM_000639.2
FAT4	NM_024582.4
FCHO1	NM_001161357.1
FERMT1	NM_017671.4
FERMT3	NM_031471.5
FOXI3	NM_001135649.2
FOXN1	NM_003593.2
FOXP3	NM_014009.3
FPR1	NM_002029.3
G6PC	NM_000151.3
G6PC3	NM_138387.3
G6PD	NM_001042351.2
GATA2	NM_032638.4
GFI1	NM_005263.3

GENE	TRANSCRIPT
GINS1	NM_021067.4
GTF2E2	NM_002095.4
GTF2H5	NM_207118.2
GUCY2C	NM_004963.3
HAX1	NM_006118.3
HELLS	NM_018063.4
HMOX1	NM_002133.2
HPS1	NM_000195.4
HPS3	NM_032383.4
HPS4	NM_022081.5
HPS5	NM_181507.1
HPS6	NM_024747.5
HTRA2	NM_013247.4
HYOU1	NM_001130991.2
ICOS	NM_012092.3
ICOSLG	NM_015259.5
IFIH1	NM_022168.3
IFNAR1	NM_000629.2
IFNAR2	NM_207585.2
IFNGR1	NM_000416.2
IFNGR2	NM_005534.3
IGLL1	NM_020070.3
IKBKB	NM_001556.2
IL10	NM_000572.2
IL10RA	NM_001558.3
IL10RB	NM_000628.4
IL12B	NM_002187.2
IL12RB1	NM_005535.2
IL12RB2	NM_001559.2
IL17F	NM_052872.3
IL17RA	NM_014339.6
IL17RC	NM_153461.3
IL1RN	NM_173841.2
IL21	NM_021803.3
IL21R	NM_021798.3
IL23R	NM_144701.2
IL2RA	NM_000417.2
IL2RB	NM_000878.3
IL2RG	NM_000206.2

GENE	TRANSCRIPT
IL36RN	NM_012275.2
IL6R	NM_000565.3
IL6ST	NM_002184.3
IL7R	NM_002185.3
IRAK4	NM_016123.3
IRF2BP2	NM_182972.2
IRF4	NM_002460.3
IRF7	NM_004031.2
IRF8	NM_002163.2
IRF9	NM_006084.4
ISG15	NM_005101.3
ITCH	NM_031483.6
ITGAM	NM_000632.3
ITGB2	NM_000211.4
ITK	NM_005546.3
JAGN1	NM_032492.3
JAK1	NM_002227.3
JAK3	NM_000215.3
KDM6A	NM_021140.3
KMT2A	NM_001197104.1
KMT2D	NM_003482.3
LAMTOR2	NM_014017.3
LAT	NM_001014987.1
LCK	NM_001042771.2
LCT	NM_002299.3
LIG1	NM_000234.2
LIG4	NM_002312.3
LIPA	NM_000235.3
LPIN2	NM_014646.2
LRBA	NM_006726.4
LRRC8A	NM_019594.3
LYN	NM_002350.3
LYST	NM_000081.3
MAGT1	NM_032121.5
MALT1	NM_006785.3
MAP3K14	NM_003954.4
MCM4	NM_005914.3
MEFV	NM_000243.2
MKL1	NM_020831.4

GENE	TRANSCRIPT
MOGS	NM_006302.2
MPLKIP	NM_138701.3
MS4A1	NM_152866.2
MSN	NM_002444.2
MTHFD1	NM_005956.3
MVK	NM_000431.3
MYD88	NM_002468.4
MYO5B	NM_001080467.2
MYSM1	NM_001085487.2
NBAS	NM_015909.3
NBN	NM_002485.4
NCF2	NM_000433.3
NCF4	NM_013416.3
NCSTN	NM_015331.2
NEUROG3	NM_020999.3
NFAT5	NM_138714.3
NFE2L2	NM_006164.4
NFKB1	NM_003998.3
NFKB2	NM_001077494.3
NFKBIA	NM_020529.2
NHEJ1	NM_024782.2
NHP2	NM_017838.3
NLRC4	NM_021209.4
NLRP1	NM_033004.3
NLRP12	NM_144687.3
NLRP3	NM_004895.4
NOD2	NM_022162.2
NOP10	NM_018648.3
NSMCE3	NM_138704.3
OAS1	NM_016816.3
ORAI1	NM_032790.3
OSTM1	NM_014028.3
OTULIN	NM_138348.4
PARN	NM_002582.3
PAX1	NM_006192.4
PEPD	NM_000285.3
PGM3	NM_001199917.1
PIK3CD	NM_005026.3
PIK3R1	NM_181523.2

GENE	TRANSCRIPT
PLCG2	NM_002661.4
PMM2	NM_000303.2
PNP	NM_000270.3
POLA1	NM_016937.3
POLD1*	NM_002691.3
POLE	NM_006231.3
POLE2	NM_002692.3
POLR3A	NM_007055.3
POMP	NM_015932.5
PRF1	NM_001083116.1
PRKCD	NM_006254.3
PRKDC	NM_006904.6
PSENEN	NM_172341.2
PSMA3	NM_002788.3
PSMB4	NM_002796.2
PSMB8	NM_148919.3
PSMG2	NM_020232.4
PSTPIP1	NM_003978.3
PTPRC*	NM_002838.4
RAB27A	NM_004580.4
RAC2	NM_002872.4
RAG1	NM_000448.2
RAG2	NM_000536.3
RANBP2*	NM_006267.4
RASGRP1	NM_005739.3
RBCK1	NM_031229.3
RELA	NM_021975.3
RELB	NM_006509.3
RFX5	NM_000449.3
RFXANK	NM_003721.3
RFXAP	NM_000538.3
RHOH	NM_004310.4
RIPK1	NM_003804.4
RMRP	NR_003051.3
RNASEH2A	NM_006397.2
RNASEH2B	NM_024570.3
RNASEH2C	NM_032193.3
RNF113A	NM_006978.2
RNF168	NM_152617.3

GENE	TRANSCRIPT
RNF31	NM_017999.4
RNU4ATAC	NR_023343.1
RORC	NM_005060.3
RPSA	NM_002295.5
RTEL1	NM_001283009.1
SAMD9	NM_017654.3
SAMD9L	NM_152703.4
SAMHD1	NM_015474.3
SAR1B	NM_001033503.2
SCO2	NM_005138.2
SEC61A1	NM_013336.3
SEMA3E	NM_012431.2
SERPING1	NM_000062.2
SH2D1A	NM_002351.4
SH3BP2	NM_003023.4
SH3KBP1	NM_031892.2
SI*	NM_001041.3
SIAE	NM_170601.4
SKIV2L	NM_006929.4
SLC26A3	NM_000111.2
SLC29A3	NM_018344.5
SLC35C1	NM_018389.4
SLC37A4	NM_001164277.1
SLC39A7	NM_001077516.1
SLC46A1	NM_080669.5
SLC5A1	NM_000343.3
SLC7A7	NM_001126106.2
SLC9A3*	NM_004174.3
SLX4	NM_032444.2
SMARCAL1	NM_014140.3
SMARCD2	NM_001098426.1
SNX10	NM_001199835.1
SP110	NM_004509.3
SPINK5	NM_006846.3
SPINT2	NM_021102.3
SPPL2A	NM_032802.3
SRP54	NM_003136.3
SRP72	NM_006947.3
STAT1	NM_007315.3

GENE	TRANSCRIPT
STAT2	NM_005419.3
STAT3	NM_139276.2
STAT4	NM_003151.3
STAT5B*	NM_012448.3
STIM1	NM_003156.3
STK4	NM_006282.3
STN1	NM_024928.4
STX11	NM_003764.3
STX3	NM_004177.4
STXBP2	NM_006949.3
TAOK2	NM_016151.3
TAP1	NM_000593.5
TAP2	NM_000544.3
TAPBP	NM_003190.4
TAZ	NM_000116.4
TBX1	NM_080647.1
TCF3	NM_003200.4;NM_001136139.3
TCIRG1	NM_006019.3
TCN2	NM_000355.3
TERC	NR_001566.1
TERT	NM_198253.2
TFRC	NM_003234.3
TGFB1	NM_000660.5
TGFBR1	NM_004612.2
TGFBR2	NM_003242.5
THBD	NM_000361.2
TICAM1	NM_182919.3
TIMM50	NM_001001563.3
TINF2	NM_001099274.1
TLR3	NM_003265.2
TMC6	NM_007267.7
TMC8	NM_152468.4
TMEM173	NM_198282.3
TNFAIP3	NM_006290.3
TNFRSF11A	NM_003839.3
TNFRSF13B	NM_012452.2
TNFRSF13C	NM_052945.3
TNFRSF1A	NM_001065.3
TNFRSF4	NM_003327.3

GENE	TRANSCRIPT
TNFRSF6B	NM_003823.3
TNFRSF9	NM_001561.5
TNFSF11	NM_003701.3
TNFSF12	NM_003809.2
TONSL	NM_013432.4
TOP2B	NM_001068.3
TP63	NM_003722.4
TPP2	NM_003291.2
TRAF3	NM_003300.3
TRAF3IP2	NM_147686.3
TREX1	NM_033629.4
TRNT1	NM_182916.2
TTC37	NM_014639.3
TTC7A	NM_020458.3
TYK2	NM_003331.4
UNC13D	NM_199242.2
UNC45A	NM_018671.4
UNC93B1	NM_030930.3
UNG	NM_080911.2
USB1	NM_024598.3
VAV1	NM_005428.3
VPS13B	NM_017890.4
VPS45	NM_007259.4
WAS	NM_000377.2
WDR1	NM_017491.3
WIPF1	NM_001077269.1
WRAP53	NM_018081.2
XIAP	NM_001167.3
ZAP70	NM_001079.3
ZBTB24	NM_014797.2
ZCCHC8	NM_017612.4
ZNF341	NM_032819.4

Methods

- Genomic DNA obtained from the submitted sample is enriched for targeted regions using a hybridization-based protocol, and sequenced using Illumina technology. Unless otherwise indicated, all targeted regions are sequenced with ≥50x depth or are supplemented with additional analysis. Reads are aligned to a reference sequence (GRCh37), and sequence changes are identified and interpreted in the context of a single clinically relevant transcript, indicated below. Enrichment and analysis focus on the coding sequence of the indicated transcripts, 20bp of flanking intronic sequence, and other specific genomic regions demonstrated to be causative of disease at the time of assay design. Promoters, untranslated regions, and other non-coding regions are not otherwise interrogated. For some genes only targeted loci are analyzed (indicated in the table above). Exonic deletions and duplications are called using an in-house algorithm that determines copy number at each target by comparing the read depth for each target in the proband sequence with both mean read-depth and read-depth distribution, obtained from a set of clinical samples. Markers across the X and Y chromosomes are analyzed for quality control purposes and may detect deviations from the expected sex chromosome complement. Such deviations may be included in the report in accordance with internal guidelines. All clinically significant observations are confirmed by orthogonal technologies, except individually validated variants and variants previously confirmed in a first-degree relative. Confirmation technologies include any of the following: Sanger sequencing, Pacific Biosciences SMRT sequencing, MLPA, MLPA-seq, Array CGH. Array CGH confirmation of NGS CNV calling performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103, #05D2040778). The following analyses are performed if relevant to the requisition. For PMS2 exons 12-15, the reference genome has been modified to force all sequence reads derived from PMS2 and the PMS2CL pseudogene to align to PMS2, and variant calling algorithms are modified to support an expectation of 4 alleles. If a rare SNP or indel variant is identified by this method, both PMS2 and the PMS2CL pseudogene are amplified by long-range PCR and the location of the variant is determined by Pacific Biosciences (PacBio) SMRT sequencing of the relevant exon in both long-range amplicons. If a CNV is identified, MLPA or MLPA-seq is run to confirm the variant. If confirmed, both PMS2 and PMS2CL are amplified by long-range PCR, and the identity of the fixed differences between PMS2 and PMS2CL are sequenced by PacBio from the long-range amplicon to disambiguate the location of the CNV. Technical component of confirmatory sequencing is performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103, #05D2040778). Technical component of Fibroblast cell-culturing and gDNA extraction from skin punch biopsy is performed by Invitae Corporation (5 Technology Drive, Irvine CA 92618, #05D1052995).
- A PMID is a unique identifier referring to a published, scientific paper. Search by PMID at http://www.ncbi.nlm.nih.gov/pubmed.
- An rsID is a unique identifier referring to a single genomic position, and is used to associate population frequency information with sequence changes at that position. Reported population frequencies are derived from a number of public sites that aggregate data from large-scale population sequencing projects, including ExAC (http://exac.broadinstitute.org), gnomAD (http://gnomad.broadinstitute.org), and dbSNP (http://ncbi.nlm.nih.gov/SNP).
- A MedGen ID is a unique identifier referring to an article in MedGen, NCBI's centralized database of information about genetic disorders and phenotypes. Search by MedGen ID at http://www.ncbi.nlm.nih.gov/medgen. An OMIM number is a unique identifier referring to a comprehensive entry in Online Mendelian Inheritance of Man (OMIM). Search by OMIM number at http://omim.org/.
- Invitae uses information from individuals undergoing testing to inform variant interpretation. If "Invitae" is cited as a reference in the variant details this may refer to the individual in this requisition and/or historical internal observations.

Limitations

Based on validation study results, this assay achieves >99% analytical sensitivity and specificity for single nucleotide variants, insertions and deletions <15bp in length, and exon-level deletions and duplications. Invitae's methods also detect insertions and deletions larger than 15bp but smaller than a full exon but sensitivity for these may be marginally reduced. Invitae's deletion/duplication analysis determines copy number at a single exon resolution at virtually all targeted exons. However, in rare situations, single-exon copy number events may not be analyzed due to inherent sequence properties or isolated reduction in data quality. Certain types of variants, such as structural rearrangements (e.g. inversions, gene conversion events, translocations, etc.) or variants embedded in sequence with complex architecture (e.g. short tandem repeats or segmental duplications), may not be detected. Additionally, it may not be possible to fully resolve certain details about variants, such as mosaicism, phasing, or mapping ambiguity. Unless explicitly guaranteed, sequence changes in the promoter, non-coding exons, and other non-coding regions are not covered by this assay. Please consult the test definition on our website for details regarding regions or types of variants that are covered or excluded for this test. This report reflects the analysis of an extracted genomic DNA sample. In very rare cases (such as circulating hematolymphoid neoplasm, bone marrow transplant, recent blood transfusion, or maternal cell contamination), the analyzed DNA may not represent the patient's constitutional genome.

FANCL: Sequencing analysis for exons 4 includes only cds +/- 10 bp. RANBP2: Deletion/duplication and sequencing analysis is not offered for exons 1-11, 15-29. CSF2RA: Deletion/duplication analysis is not offered for this gene. CFH: Deletion/duplication analysis is not offered for exons 20, 22 and sequencing analysis is not offered for exons 15, 20, 22. SI: Deletion/duplication analysis is not offered for exon 7. CORO1A: Deletion/duplication and sequencing analysis is not offered for exon 11. DUOX2: Deletion/duplication and sequencing analysis is not offered for exons 6-7. ATM: Sequencing analysis for exons 24 includes only cds +/- 10 bp. SLC9A3: Deletion/duplication analysis is not offered for exon 8. PTPRC: Sequencing analysis is not offered for exons 3, 15. POLD1: Sequencing analysis for exons 22 includes only cds +/- 10 bp. STAT5B: Deletion/duplication and sequencing analysis is not offered for exons 7-8. EFL1: Deletion/duplication and sequencing analysis is not offered for exons 7, 15.

For Addended, Amended and Corrected reports, orthogonal confirmation may not have been performed on variants that would have otherwise met criteria for confirmation at the time of the original analysis.

Disclaimer

DNA studies do not constitute a definitive test for the selected condition(s) in all individuals. It should be realized that there are possible sources of error. Errors can result from trace contamination, rare technical errors, rare genetic variants that interfere with analysis, recent scientific developments, and alternative classification systems. This test should be one of many aspects used by the healthcare provider to help with a diagnosis and treatment plan, but it is not a diagnosis itself. This test was developed and its performance characteristics determined by Invitae. It has not been cleared or approved by the FDA. The laboratory is regulated under the Clinical Laboratory Improvement Act (CLIA) as qualified to perform high-complexity clinical tests (CLIA ID: 05D2040778). This test is used for clinical purposes. It should not be regarded as investigational or for research.

This report has been reviewed and approved by:

Jennifer Sanmann, Ph.D., FACMG
Clinical Molecular Geneticist & Clinical Cytogeneticist

INVITAE

GENERAL GUIDELINES
POSITIVE RESULTS GUIDE: ATM

This document is not part of Invitae's clinical report and does not represent medical advice. These are general guidelines that are not specific to your result and may not represent all relevant international recommendations. You can use this guide to talk to your healthcare provider about your test results, clinical history, and the most current guidelines. This guide may not be appropriate for results that are suspected to be blood-limited, possibly mosaic, or suggestive of a larger imbalance of genetic material. Invitae recognizes that individuals have diverse gender and sexual identities. In this guide, the terms female, male, women, and men refer to sex assigned at birth.

What is a positive ATM result?

A positive test result means that a genetic change (variant) was found in the ATM gene. A positive ATM variant is considered "pathogenic" or "likely pathogenic" because it is associated with an increased chance for certain types of cancer.

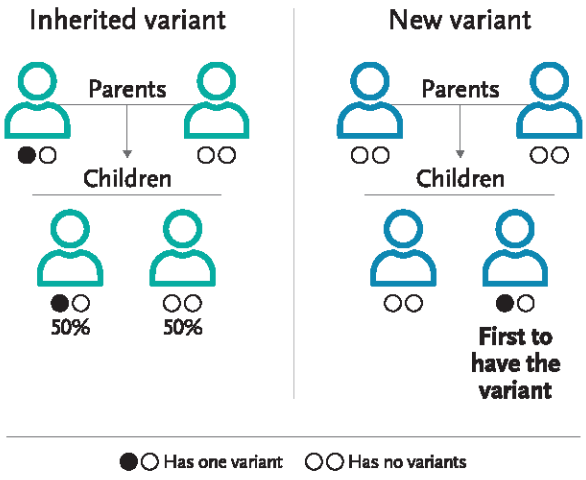
What does this mean?

It is possible for anyone to get cancer at some point in their life, however, individuals who are born with an ATM variant have a higher risk of developing certain cancers compared to the average person. There is an increased chance for female breast cancer (21-33%). ATM is also associated with ovarian cancer, pancreatic cancer and prostate cancer, however, the lifetime risks are not clear. Types of cancer and age of onset can vary, and some individuals may never develop cancers. Individuals may have different conditions or symptoms depending on whether they inherit one or two variants in ATM. Some people inherit two ATM variants, which may cause a rare condition called ataxia-telangiectasia. Sometimes an ATM variant is acquired later in life within the blood, which is known as clonal hematopoiesis. The likelihood of clonal hematopoiesis increases with an individual's age, exposure to chemotherapy, or radiation treatment. Management will differ depending on whether the variant was present at birth or acquired in the blood later on.

What does this mean for family members?

Relatives should be informed about these results. It is recommended that family members talk with their own healthcare provider about a plan for genetic testing and/or health screening. Genetic testing is a personal choice and some individuals may choose not to have genetic testing. Laws protecting employment and health insurance may apply to individuals undergoing genetic testing (for example, the Genetic Information Nondiscrimination Act in the United States).

Will family members have the same variant(s)?
The image shows where a ATM variant may have come from. Any individual can inherit and pass on a ATM variant, regardless of sex.



ATM variants can be inherited from a parent or an individual may be the first person in the family to have a new ATM variant. Genetic testing of parents may help determine the risk to the individual's siblings and other relatives. Individuals with an ATM variant present from birth can pass it on to children. ATM-related cancer usually does not affect children. Genetic testing for an ATM variant is not typically indicated until age 18 or older.

For individuals who are planning a family, reproductive options may be available to help lower the chance of passing on a variant to children.

Create a plan with a healthcare provider

These options are a guide for an individual and their healthcare provider. They are meant to be used along with an individual's genetic test results and other health information as part of a discussion to make a personalized care plan. Each option may or may not be right for an individual. A positive test result on its own cannot predict how a condition may affect an individual. This guide may not be appropriate for results that are suspected to be blood-limited, possibly mosaic, or suggestive of a larger imbalance of genetic material.

Options to consider

TOPIC	OPTION	MORE INFORMATION
Clinical assessment	• Assess whether the ATM variant is more likely to have been present from birth (which causes an increased risk for cancer) or acquired later in the blood (clonal hematopoiesis). • Consider the personal or family history of cancer, the individual's age, and history of chemotherapy, radiation treatment, or a blood disorder to help determine the most likely explanation. • This guide provides resources for management of individuals with an ATM variant present from birth.	• If the underlying reason for the result is not clear, consider additional steps to clarify the nature of this variant. ◦ If the original sample type was blood, saliva, or cheek swab, consider testing DNA from a different sample type, such as a skin biopsy. ◦ Consider testing family members. • If the variant is found in a different sample type or in family members, it suggests that the individual was born with the ATM variant.
Breast cancer	• Mammogram every year starting at age 40 and consider breast MRI with contrast every year starting at age 30-35, or 5-10 years before the earliest known breast cancer in the family (whichever comes first). (1)	• Women treated for breast cancer who have not undergone a bilateral mastectomy should continue these breast screening recommendations. (1)
	• There is insufficient evidence to recommend risk-reducing bilateral mastectomy (surgery to remove the breasts) for all ATM-positive women, but it may be considered based on personal and family history. (1)	
Pancreatic cancer	• Screening should be considered for individuals with a family history of pancreatic cancer (exocrine) in a first- or second-degree relative on the same side (or presumed to be on the same side) of the family as the ATM variant. (1) • For these individuals, consider pancreatic imaging with contrast-enhanced MRI/magnetic resonance cholangiopancreatography (MRCP) and/or endoscopic ultrasound (EUS) every year starting at age 50, or 10 years before the earliest known pancreatic cancer in the family (whichever comes first). (1)	• This screening should be performed in an experienced high-volume center. (1)
Ovarian cancer	• There is insufficient evidence to recommend risk reducing salpingo-oophorectomy (surgery to remove the ovaries and fallopian tubes) for all ATM-positive women at this time, but it may be considered based on personal medical and family history. (1)	
Prostate cancer	• Consider prostate-specific antigen (PSA) screening every year starting at age 40. (2)	• Personal and family history can inform when to begin shared decision-making regarding prostate cancer screening. (2)
	• Consider digital rectal examination when PSA testing is done. (2)	

TOPIC	OPTION	MORE INFORMATION
Colorectal cancer	• Currently there is insufficient evidence to recommend specialized colorectal cancer screening for ATM positive individuals. (3) • Screening for colorectal cancer should be based on personal and family history. (3)	
Family planning	• Discuss reproductive risks. (4) • Individuals with an ATM variant have a 50% chance to pass on the variant to a child.	• Preconception and prenatal reproductive options are available and could be discussed in more detail with a reproductive specialist.
	• Individuals with an ATM variant may also have an increased chance to have a child with ataxia-telangiectasia, if their reproductive partner also has a positive ATM variant.	• Ataxia-telangiectasia is a rare, childhood onset condition that affects many different parts of the body. Common symptoms include uncoordinated movements (ataxia), problems with the nervous system, clusters of enlarged blood vessels (telangiectasias), weakened immune system, frequent infections, sensitivity to radiation, and a higher than normal risk to develop certain cancers such as leukemia and lymphoma.
	• An individual's reproductive partner can consider genetic testing to help determine the risk of a child inheriting two ATM variants and having ataxia-telangiectasia. (4)	• If an individual's reproductive partner also has a positive ATM variant, there would be a 25% chance to have a child with ataxia-telangiectasia.

These options include recommendations from NCCN (1,2,3) and PMID: 28225426 (4). Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Version 2.2023 (1) © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed 01/19/2023. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer Early Detection Version 1.2023 (2). © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed 01/23/2023. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Colorectal Version 1.2023 (3). © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed 05/30/2023. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. More information about genetics and disease continues to be available, so please always refer to the current guidelines and recommendations when considering surveillance and treatment options. Information on this document may not include all relevant international recommendations and acts as a supplement to the Invitae result report. This information is not meant to replace a discussion with an individual's healthcare provider and should not be considered or interpreted as medical advice. Additional resources provided within this document do not indicate or imply any endorsement by Invitae with respect to any third party or any website or the products or services offered by any third party.

Resources

Genetic counseling can help individuals understand their genetic test results and options for next steps. Reviewing test results with a genetic counselor or other healthcare provider is recommended. Local or telehealth genetic counselors can be identified using the Find a Genetic Counselor search tool at nsgc.org (US and Canada). Individuals who had genetic testing through Invitae can also log in to their patient portal (invitae.com) to view their results, contact a genetic counselor, or join Invitae's Patient Insights Network (PIN), an online platform where individuals can share information about their health and experiences to help advance research and drug development.

Notes for personalized assessment

INVITAE

INVITAE DIAGNOSTIC TESTING RESULTS

Patient name:	John R Zoubek	**Sample type:**	Saliva	**Report date:**	03/25/2021
DOB:	12/20/1979	**Sample collection date:**	02/23/2021	**Invitae #:**	RQ2026347
Sex:	Male	**Sample accession date:**	02/27/2021	**Clinical team:**	GC HIS Lisa Schimmenti
MRN:	12-097-059				

Reason for testing

Diagnostic test for a personal history of disease

Test performed

Sequence analysis and deletion/duplication testing of the 407 genes listed in the Genes Analyzed section.

- Invitae Primary Immunodeficiency Panel

RESULT: POSITIVE

One Likely Pathogenic variant identified in ATM. ATM is associated with autosomal dominant predisposition to certain cancers and autosomal recessive ataxia-telangiectasia.

Additional Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
ATM	c.2922-50_2940del (Splice site)	heterozygous	Likely Pathogenic
ICOSLG	c.866C>T (p.Ala289Val)	heterozygous	Uncertain Significance

About this test

This diagnostic test evaluates 407 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

Next steps

- This is a medically important result that should be discussed with a healthcare provider, such as a genetic counselor, to learn more about this result and the appropriate next steps for further evaluation, treatment and/or management. This result should be interpreted within the context of additional laboratory results, family history and clinical findings.
- Please see NCCN (www.nccn.org) for management guidelines regarding ATM-related condition(s).
- Consider sharing this result with relatives as they may also be at risk. Details on our Family Variant Testing program can be found at www.invitae.com/family.
- Register your test at www.invitae.com/patients to download a digital copy of your results. You can also access educational resources about how your results can help inform your health.

Laboratory Director: Kristin Gibson, PhD, FACMG, NYCQ, CGMB, ErCLG
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Clinical summary

A Likely Pathogenic variant, c.2922-50_2940del (Splice site), was identified in ATM.

- The ATM gene is associated with autosomal dominant predisposition to breast, pancreatic (PMID: 26483394) and possibly prostate cancer (PMID: 27989354, 28657667) in addition to autosomal recessive ataxia-telangiectasia (A-T) (MedGen UID: 439). There is also preliminary evidence suggesting ATM is associated with autosomal dominant predisposition to other cancer types including stomach (PMID: 30657113), ovarian (PMID: 28888541, 30733081), bladder (PMID: 26662178, 31844177) and colon (PMID: 30862463); although available evidence is insufficient to make a determination regarding these relationships.
- This result is consistent with a predisposition to, or diagnosis of, autosomal dominant ATM-related conditions.
- The lifetime risk of breast cancer in females with one pathogenic ATM variant is approximately 17-33% (PMID: 15928302, 27112364). There is also an increased risk of pancreatic and prostate cancer; however, lifetime cancer risks are not established (PMID: 22585167, 26098866, 26483394, 27433846, 27324988, 27989354).

  A-T is characterized by progressive cerebellar ataxia beginning in early childhood, oculomotor apraxia, choreoathetosis, telangiectasias of the conjunctivae, immunodeficiency, frequent infections, and increased malignancy risk, particularly leukemia and lymphoma (PMID: 15279807, 26050521).
- Biological relatives have a chance of being at risk for autosomal dominant ATM-related conditions and have a chance of being carriers for autosomal recessive ATM-related conditions. Those at risk should consider testing.

A Variant of Uncertain Significance, c.866C>T (p.Ala289Val), was identified in ICOSLG.

- The ICOSLG gene currently has no well-established disease association; however, there is preliminary evidence supporting a correlation with autosomal recessive combined immunodeficiency (PMID: 30498080).
- Not all variants present in a gene cause disease. The clinical significance of the variant(s) identified in this gene is uncertain. Until this uncertainty can be resolved, caution should be exercised before using this result to inform clinical management decisions.
- Familial VUS testing is not offered. Testing family members for this variant will not contribute evidence to allow variant reclassification. Details on our VUS Resolution and Family Variant Testing Programs can be found at https://www.invitae.com/family.

Variant details

ATM, Exon 20, c.2922-50_2940del (Splice site), heterozygous, Likely Pathogenic

- This variant results in the deletion of part of exon 20 (c.2922-50_2940del) of the ATM gene. It is expected to disrupt RNA splicing. Variants that disrupt the donor or acceptor splice site typically lead to a loss of protein function (PMID: 16199547), and loss-of-function variants in ATM are known to be pathogenic (PMID: 23807571, 25614872).
- This variant has not been reported in the literature in individuals with ATM-related conditions. ClinVar contains an entry for this variant (Variation ID: 407642).
- In summary, the currently available evidence indicates that the variant is pathogenic, but additional data are needed to prove that conclusively. Therefore, this variant has been classified as Likely Pathogenic.

ICOSLG, Exon 6, c.866C>T (p.Ala289Val), heterozygous, Uncertain Significance

- This sequence change replaces alanine with valine at codon 289 of the ICOSLG protein (p.Ala289Val). The alanine residue is weakly conserved and there is a small physicochemical difference between alanine and valine.
- While this variant is present in population databases (rs199878735), the frequency information is unreliable, as metrics indicate poor data quality at this position in the ExAC database.
- This variant has not been reported in the literature in individuals with ICOSLG-related conditions.

- Algorithms developed to predict the effect of missense changes on protein structure and function output the following: SIFT: "Tolerated"; PolyPhen-2: "Benign"; Align-GVGD: "Class C0". The valine amino acid residue is found in multiple mammalian species, suggesting that this missense change does not adversely affect protein function. These predictions have not been confirmed by published functional studies and their clinical significance is uncertain.
- In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.

Genes analyzed

This table represents a complete list of genes analyzed for this individual, including the relevant gene transcript(s). If more than one transcript is listed for a single gene, variants were reported using the first transcript listed unless otherwise indicated in the report. Results are negative unless otherwise indicated in the report. Benign and Likely Benign variants are not included in this report but are available upon request. An asterisk (*) indicates that this gene has a limitation. Please see the Limitations section for details.

GENE	TRANSCRIPT
ACD	NM_001082486.1
ACP5	NM_001111035.2
ACTB	NM_001101.3
ADA	NM_000022.2
ADA2	NM_001282225.1
ADAM17	NM_003183.5
ADAR	NM_001111.4
AICDA	NM_020661.2
AIRE	NM_000383.3
AK2	NM_001625.3
ALG6	NM_013339.3
ANGPT1	NM_001146.4
ANKZF1	NM_018089.2
AP3B1	NM_003664.4
AP3D1	NM_001261826.1
ARHGEF1	NM_199002.1
ARPC1B	NM_005720.3
ASAH1	NM_177924.3
ATM*	NM_000051.3
ATP6AP1	NM_001183.5
B2M	NM_004048.2
BACH2	NM_021813.3
BCL10	NM_003921.4
BCL11B	NM_138576.3
BLM	NM_000057.3
BLNK	NM_013314.3
BLOC1S3	NM_212550.4
BLOC1S6	NM_012388.3
BTK	NM_000061.2
C17orf62	NM_001033046.3
C1QA	NM_015991.2
C1QB	NM_000491.3
C1QC	NM_172369.3
C1S	NM_201442.2
C2	NM_000063.5
C3	NM_000064.3
C5	NM_001735.2
C6	NM_000065.3
C7	NM_000587.2
C8A	NM_000562.2
C8B	NM_000066.3
C9	NM_001737.4
CARD11	NM_032415.5
CARD14	NM_024110.4
CARD8	NM_014959.3
CARD9	NM_052813.4
CARMIL2	NM_001013838.1
CASP10	NM_032977.3
CASP8	NM_001228.4
CBL	NM_005188.3
CCBE1	NM_133459.3
CD19	NM_001770.5
CD247	NM_198053.2
CD27	NM_001242.4
CD3D	NM_000732.4
CD3E	NM_000733.3
CD3G	NM_000073.2
CD40	NM_001250.5
CD40LG	NM_000074.2
CD46	NM_002389.4
CD55	NM_000574.4
CD59	NM_203330.2
CD79A	NM_001783.3
CD79B	NM_000626.3
CD81	NM_004356.3
CD8A	NM_001768.6
CDC42	NM_001791.3
CDCA7	NM_031942.4
CEBPE	NM_001805.3
CFB	NM_001710.5
CFD	NM_001928.3
CFH*	NM_000186.3
CFI	NM_000204.4
CFP	NM_002621.2
CHD7	NM_017780.3
CIB1	NM_001277764.1
CIITA	NM_000246.3
CLCN7	NM_001287.5
CLPB	NM_030813.5
COL7A1	NM_000094.3
COPA	NM_004371.3
CORO1A*	NM_007074.3
CR2	NM_001006658.2
CSF2RA*	NM_006140.4
CSF2RB	NM_000395.2
CSF3R	NM_000760.3
CTC1	NM_025099.5
CTLA4	NM_005214.4
CTPS1	NM_001905.3
CTSC	NM_001814.5
CXCR2	NM_001557.3
CXCR4	NM_003467.2
CYBA	NM_000101.3
CYBB	NM_000397.3
CYP27A1	NM_000784.3
DCLRE1C	NM_001033855.2
DDX58	NM_014314.3
DEF6	NM_022047.3
DGAT1	NM_012079.5
DIAPH1	NM_005219.4
DKC1	NM_001363.4
DNAJC21	NM_001012339.2
DNASE1L3	NM_004944.3
DNASE2	NM_001375.2
DNMT3B	NM_006892.3

GENE	TRANSCRIPT
DOCK2	NM_004946.2
DOCK8	NM_203447.3
DSG1	NM_001942.3
DTNBP1	NM_032122.4
DUOX2*	NM_014080.4
EFL1*	NM_024580.5
EIF2AK3	NM_004836.6
ELANE	NM_001972.2
EPG5	NM_020964.2
ERBIN	NM_001253697.1
ERCC2	NM_000400.3
ERCC3	NM_000122.1
ERCC6L2	NM_020207.4
EXTL3	NM_001440.3
FADD	NM_003824.3
FANCA	NM_000135.2
FANCB	NM_001018113.1
FANCE	NM_021922.2
FANCF	NM_022725.3
FANCI	NM_001113378.1
FANCL*	NM_018062.3
FAS	NM_000043.5
FASLG	NM_000639.2
FAT4	NM_024582.4
FCHO1	NM_001161357.1
FERMT1	NM_017671.4
FERMT3	NM_031471.5
FOXI3	NM_001135649.2
FOXN1	NM_003593.2
FOXP3	NM_014009.3
FPR1	NM_002029.3
G6PC	NM_000151.3
G6PC3	NM_138387.3
G6PD	NM_001042351.2
GATA2	NM_032638.4
GFI1	NM_005263.3
GINS1	NM_021067.4
GTF2E2	NM_002095.4
GTF2H5	NM_207118.2

GENE	TRANSCRIPT
GUCY2C	NM_004963.3
HAX1	NM_006118.3
HELLS	NM_018063.4
HMOX1	NM_002133.2
HPS1	NM_000195.4
HPS3	NM_032383.4
HPS4	NM_022081.5
HPS5	NM_181507.1
HPS6	NM_024747.5
HTRA2	NM_013247.4
HYOU1	NM_001130991.2
ICOS	NM_012092.3
ICOSLG	NM_015259.5
IFIH1	NM_022168.3
IFNAR1	NM_000629.2
IFNAR2	NM_207585.2
IFNGR1	NM_000416.2
IFNGR2	NM_005534.3
IGLL1	NM_020070.3
IKBKB	NM_001556.2
IL10	NM_000572.2
IL10RA	NM_001558.3
IL10RB	NM_000628.4
IL12B	NM_002187.2
IL12RB1	NM_005535.2
IL12RB2	NM_001559.2
IL17F	NM_052872.3
IL17RA	NM_014339.6
IL17RC	NM_153461.3
IL1RN	NM_173841.2
IL21	NM_021803.3
IL21R	NM_021798.3
IL23R	NM_144701.2
IL2RA	NM_000417.2
IL2RB	NM_000878.3
IL2RG	NM_000206.2
IL36RN	NM_012275.2
IL6R	NM_000565.3
IL6ST	NM_002184.3

GENE	TRANSCRIPT
IL7R	NM_002185.3
IRAK4	NM_016123.3
IRF2BP2	NM_182972.2
IRF4	NM_002460.3
IRF7	NM_004031.2
IRF8	NM_002163.2
IRF9	NM_006084.4
ISG15	NM_005101.3
ITCH	NM_031483.6
ITGAM	NM_000632.3
ITGB2	NM_000211.4
ITK	NM_005546.3
JAGN1	NM_032492.3
JAK1	NM_002227.3
JAK3	NM_000215.3
KDM6A	NM_021140.3
KMT2A	NM_001197104.1
KMT2D	NM_003482.3
LAMTOR2	NM_014017.3
LAT	NM_001014987.1
LCK	NM_001042771.2
LCT	NM_002299.3
LIG1	NM_000234.2
LIG4	NM_002312.3
LIPA	NM_000235.3
LPIN2	NM_014646.2
LRBA	NM_006726.4
LRRC8A	NM_019594.3
LYN	NM_002350.3
LYST	NM_000081.3
MAGT1	NM_032121.5
MALT1	NM_006785.3
MAP3K14	NM_003954.4
MCM4	NM_005914.3
MEFV	NM_000243.2
MKL1	NM_020831.4
MOGS	NM_006302.2
MPLKIP	NM_138701.3
MS4A1	NM_152866.2

GENE	TRANSCRIPT
MSN	NM_002444.2
MTHFD1	NM_005956.3
MVK	NM_000431.3
MYD88	NM_002468.4
MYO5B	NM_001080467.2
MYSM1	NM_001085487.2
NBAS	NM_015909.3
NBN	NM_002485.4
NCF2	NM_000433.3
NCF4	NM_013416.3
NCSTN	NM_015331.2
NEUROG3	NM_020999.3
NFAT5	NM_138714.3
NFE2L2	NM_006164.4
NFKB1	NM_003998.3
NFKB2	NM_001077494.3
NFKBIA	NM_020529.2
NHEJ1	NM_024782.2
NHP2	NM_017838.3
NLRC4	NM_021209.4
NLRP1	NM_033004.3
NLRP12	NM_144687.3
NLRP3	NM_004895.4
NOD2	NM_022162.2
NOP10	NM_018648.3
NSMCE3	NM_138704.3
OAS1	NM_016816.3
ORAI1	NM_032790.3
OSTM1	NM_014028.3
OTULIN	NM_138348.4
PARN	NM_002582.3
PAX1	NM_006192.4
PEPD	NM_000285.3
PGM3	NM_001199917.1
PIK3CD	NM_005026.3
PIK3R1	NM_181523.2
PLCG2	NM_002661.4
PMM2	NM_000303.2
PNP	NM_000270.3

GENE	TRANSCRIPT
POLA1	NM_016937.3
POLD1*	NM_002691.3
POLE	NM_006231.3
POLE2	NM_002692.3
POLR3A	NM_007055.3
POMP	NM_015932.5
PRF1	NM_001083116.1
PRKCD	NM_006254.3
PRKDC	NM_006904.6
PSENEN	NM_172341.2
PSMA3	NM_002788.3
PSMB4	NM_002796.2
PSMB8	NM_148919.3
PSMG2	NM_020232.4
PSTPIP1	NM_003978.3
PTPRC*	NM_002838.4
RAB27A	NM_004580.4
RAC2	NM_002872.4
RAG1	NM_000448.2
RAG2	NM_000536.3
RANBP2*	NM_006267.4
RASGRP1	NM_005739.3
RBCK1	NM_031229.3
RELA	NM_021975.3
RELB	NM_006509.3
RFX5	NM_000449.3
RFXANK	NM_003721.3
RFXAP	NM_000538.3
RHOH	NM_004310.4
RIPK1	NM_003804.4
RMRP	NR_003051.3
RNASEH2A	NM_006397.2
RNASEH2B	NM_024570.3
RNASEH2C	NM_032193.3
RNF113A	NM_006978.2
RNF168	NM_152617.3
RNF31	NM_017999.4
RNU4ATAC	NR_023343.1
RORC	NM_005060.3

GENE	TRANSCRIPT
RPSA	NM_002295.5
RTEL1	NM_001283009.1
SAMD9	NM_017654.3
SAMD9L	NM_152703.4
SAMHD1	NM_015474.3
SAR1B	NM_001033503.2
SCO2	NM_005138.2
SEC61A1	NM_013336.3
SEMA3E	NM_012431.2
SERPING1	NM_000062.2
SH2D1A	NM_002351.4
SH3BP2	NM_003023.4
SH3KBP1	NM_031892.2
SI*	NM_001041.3
SIAE	NM_170601.4
SKIV2L	NM_006929.4
SLC26A3	NM_000111.2
SLC29A3	NM_018344.5
SLC35C1	NM_018389.4
SLC37A4	NM_001164277.1
SLC39A7	NM_001077516.1
SLC46A1	NM_080669.5
SLC5A1	NM_000343.3
SLC7A7	NM_001126106.2
SLC9A3*	NM_004174.3
SLX4	NM_032444.2
SMARCAL1	NM_014140.3
SMARCD2	NM_001098426.1
SNX10	NM_001199835.1
SP110	NM_004509.3
SPINK5	NM_006846.3
SPINT2	NM_021102.3
SPPL2A	NM_032802.3
SRP54	NM_003136.3
SRP72	NM_006947.3
STAT1	NM_007315.3
STAT2	NM_005419.3
STAT3	NM_139276.2
STAT4	NM_003151.3

GENE	TRANSCRIPT
STAT5B*	NM_012448.3
STIM1	NM_003156.3
STK4	NM_006282.3
STN1	NM_024928.4
STX11	NM_003764.3
STX3	NM_004177.4
STXBP2	NM_006949.3
TAOK2	NM_016151.3
TAP1	NM_000593.5
TAP2	NM_000544.3
TAPBP	NM_003190.4
TAZ	NM_000116.4
TBX1	NM_080647.1
TCF3	NM_003200.4;NM_001136139.3
TCIRG1	NM_006019.3
TCN2	NM_000355.3
TERC	NR_001566.1
TERT	NM_198253.2
TFRC	NM_003234.3
TGFB1	NM_000660.5
TGFBR1	NM_004612.2
TGFBR2	NM_003242.5
THBD	NM_000361.2
TICAM1	NM_182919.3
TIMM50	NM_001001563.3
TINF2	NM_001099274.1
TLR3	NM_003265.2
TMC6	NM_007267.7
TMC8	NM_152468.4
TMEM173	NM_198282.3
TNFAIP3	NM_006290.3
TNFRSF11A	NM_003839.3
TNFRSF13B	NM_012452.2
TNFRSF13C	NM_052945.3
TNFRSF1A	NM_001065.3
TNFRSF4	NM_003327.3
TNFRSF6B	NM_003823.3
TNFRSF9	NM_001561.5
TNFSF11	NM_003701.3

GENE	TRANSCRIPT
TNFSF12	NM_003809.2
TONSL	NM_013432.4
TOP2B	NM_001068.3
TP63	NM_003722.4
TPP2	NM_003291.2
TRAF3	NM_003300.3
TRAF3IP2	NM_147686.3
TREX1	NM_033629.4
TRNT1	NM_182916.2
TTC37	NM_014639.3
TTC7A	NM_020458.3
TYK2	NM_003331.4
UNC13D	NM_199242.2
UNC45A	NM_018671.4
UNC93B1	NM_030930.3
UNG	NM_080911.2
USB1	NM_024598.3
VAV1	NM_005428.3
VPS13B	NM_017890.4
VPS45	NM_007259.4
WAS	NM_000377.2
WDR1	NM_017491.3
WIPF1	NM_001077269.1
WRAP53	NM_018081.2
XIAP	NM_001167.3
ZAP70	NM_001079.3
ZBTB24	NM_014797.2
ZCCHC8	NM_017612.4
ZNF341	NM_032819.4

Methods

- Genomic DNA obtained from the submitted sample is enriched for targeted regions using a hybridization-based protocol, and sequenced using Illumina technology. Unless otherwise indicated, all targeted regions are sequenced with ≥50x depth or are supplemented with additional analysis. Reads are aligned to a reference sequence (GRCh37), and sequence changes are identified and interpreted in the context of a single clinically relevant transcript, indicated below. Enrichment and analysis focus on the coding sequence of the indicated transcripts, 20bp of flanking intronic sequence, and other specific genomic regions demonstrated to be causative of disease at the time of assay design. Promoters, untranslated regions, and other non-coding regions are not otherwise interrogated. For some genes only targeted loci are analyzed (indicated in the table above). Exonic deletions and duplications are called using an in-house algorithm that determines copy number at each target by comparing the read depth for each target in the proband sequence with both mean read-depth and read-depth distribution, obtained from a set of clinical samples. Markers across the X and Y chromosomes are analyzed for quality control purposes and may detect deviations from the expected sex chromosome complement. Such deviations may be included in the report in accordance with internal guidelines. All clinically significant observations are confirmed by orthogonal technologies, except individually validated variants and variants previously confirmed in a first-degree relative. Confirmation technologies include any of the following: Sanger sequencing, Pacific Biosciences SMRT sequencing, MLPA, MLPA-seq, Array CGH. Array CGH confirmation of NGS CNV calling performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103, #05D2040778). The following analyses are performed if relevant to the requisition. For PMS2 exons 12-15, the reference genome has been modified to force all sequence reads derived from PMS2 and the PMS2CL pseudogene to align to PMS2, and variant calling algorithms are modified to support an expectation of 4 alleles. If a rare SNP or indel variant is identified by this method, both PMS2 and the PMS2CL pseudogene are amplified by long-range PCR and the location of the variant is determined by Pacific Biosciences (PacBio) SMRT sequencing of the relevant exon in both long-range amplicons. If a CNV is identified, MLPA or MLPA-seq is run to confirm the variant. If confirmed, both PMS2 and PMS2CL are amplified by long-range PCR, and the identity of the fixed differences between PMS2 and PMS2CL are sequenced by PacBio from the long-range amplicon to disambiguate the location of the CNV. Technical component of confirmatory sequencing is performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103, #05D2040778). Technical component of Fibroblast cell-culturing and gDNA extraction from skin punch biopsy is performed by Invitae Corporation (5 Technology Drive, Irvine CA 92618, #05D1052995).
- A PMID is a unique identifier referring to a published, scientific paper. Search by PMID at http://www.ncbi.nlm.nih.gov/pubmed.
- An rsID is a unique identifier referring to a single genomic position, and is used to associate population frequency information with sequence changes at that position. Reported population frequencies are derived from a number of public sites that aggregate data from large-scale population sequencing projects, including ExAC (http://exac.broadinstitute.org), gnomAD (http://gnomad.broadinstitute.org), and dbSNP (http://ncbi.nlm.nih.gov/SNP).
- A MedGen ID is a unique identifier referring to an article in MedGen, NCBI's centralized database of information about genetic disorders and phenotypes. Search by MedGen ID at http://www.ncbi.nlm.nih.gov/medgen. An OMIM number is a unique identifier referring to a comprehensive entry in Online Mendelian Inheritance of Man (OMIM). Search by OMIM number at http://omim.org/.
- Invitae uses information from individuals undergoing testing to inform variant interpretation. If "Invitae" is cited as a reference in the variant details this may refer to the individual in this requisition and/or historical internal observations.

Limitations

Based on validation study results, this assay achieves >99% analytical sensitivity and specificity for single nucleotide variants, insertions and deletions <15bp in length, and exon-level deletions and duplications. Invitae's methods also detect insertions and deletions larger than 15bp but smaller than a full exon but sensitivity for these may be marginally reduced. Invitae's deletion/duplication analysis determines copy number at a single exon resolution at virtually all targeted exons. However, in rare situations, single-exon copy number events may not be analyzed due to inherent sequence properties or isolated reduction in data quality. Certain types of variants, such as structural rearrangements (e.g. inversions, gene conversion events, translocations, etc.) or variants embedded in sequence with complex architecture (e.g. short tandem repeats or segmental duplications), may not be detected. Additionally, it may not be possible to fully resolve certain details about variants, such as mosaicism, phasing, or mapping ambiguity. Unless explicitly guaranteed, sequence changes in the promoter, non-coding exons, and other non-coding regions are not covered by this assay. Please consult the test definition on our website for details regarding regions or types of variants that are covered or excluded for this test. This report reflects the analysis of an extracted genomic DNA sample. In very rare cases (such as circulating hematolymphoid neoplasm, bone marrow transplant, recent blood transfusion, or maternal cell contamination), the analyzed DNA may not represent the patient's constitutional genome.

Laboratory Director: Kristin Gibson, PhD, FACMG, NYCQ, CGMB, ErCLG
Invitae 1400 16th Street, San Francisco, CA 94103 · clientservices@invitae.com · 800.436.3037

FANCL: Sequencing analysis for exons 4 includes only cds +/- 10 bp. RANBP2: Deletion/duplication and sequencing analysis is not offered for exons 1-11, 15-29. CSF2RA: Deletion/duplication analysis is not offered for this gene. CFH: Deletion/duplication analysis is not offered for exons 20, 22 and sequencing analysis is not offered for exons 15, 20, 22. SI: Deletion/duplication analysis is not offered for exon 7. CORO1A: Deletion/duplication and sequencing analysis is not offered for exon 11. DUOX2: Deletion/duplication and sequencing analysis is not offered for exons 6-7. ATM: Sequencing analysis for exons 24 includes only cds +/- 10 bp. SLC9A3: Deletion/duplication analysis is not offered for exon 8. PTPRC: Sequencing analysis is not offered for exons 3, 15. POLD1: Sequencing analysis for exons 22 includes only cds +/- 10 bp. STAT5B: Deletion/duplication and sequencing analysis is not offered for exons 7-8. EFL1: Deletion/duplication and sequencing analysis is not offered for exons 7, 15.

Disclaimer

DNA studies do not constitute a definitive test for the selected condition(s) in all individuals. It should be realized that there are possible sources of error. Errors can result from trace contamination, rare technical errors, rare genetic variants that interfere with analysis, recent scientific developments, and alternative classification systems. This test should be one of many aspects used by the healthcare provider to help with a diagnosis and treatment plan, but it is not a diagnosis itself. This test was developed and its performance characteristics determined by Invitae. It has not been cleared or approved by the FDA. The laboratory is regulated under the Clinical Laboratory Improvement Act (CLIA) as qualified to perform high-complexity clinical tests (CLIA ID: 05D2040778). This test is used for clinical purposes. It should not be regarded as investigational or for research.

This report has been reviewed and approved by:

Christina Y. Hung, MD, FACMG
Clinical Molecular and Biochemical Geneticist

INVITAE

GENERAL GUIDELINES
POSITIVE RESULTS GUIDE: ATM

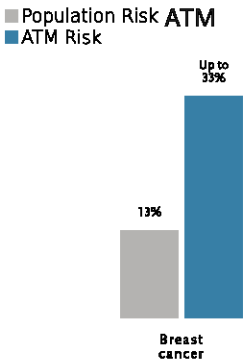
This document is not part of Invitae's clinical report and does not represent medical advice. These are general guidelines that are not specific to your result. You can use this guide to talk to your healthcare provider about your test results, clinical history, and the most current guidelines.

What is a positive ATM result?

A positive test result means that you have a genetic change, called a pathogenic or likely pathogenic variant ("mutation"), in your ATM gene. This variant can cause cancer.

What does this mean?

It's possible for anyone to get cancer at some point in their life, however, people with an ATM variant have a higher risk of developing breast, pancreatic, and possibly prostate and ovarian cancer. People with one variant in the ATM gene may develop cancer. Some people inherit two variants and can have a rare condition called ataxia-telangiectasia. See the table later in this guide for ways to find and manage these cancers.



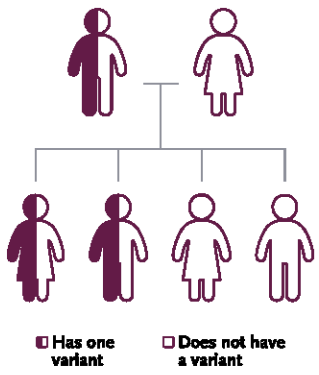
What does this mean for family members?

Genes and variants are passed from generation to generation. Your relatives may also have the same variant(s) in ATM. Both men and women can inherit and pass on this type of variant.

Who should be tested next?
Your close relatives have a chance of also having the same positive variant. This means your parents, siblings, and children. Your other relatives may also have the same ATM variant(s). People with variants in ATM have different conditions or symptoms depending on whether they inherit one or two variants.

Inheriting this ATM variant does not mean that a person will definitely develop cancer. An ATM variant affects everyone differently. Family members may develop the condition at different ages, or they may develop different features. These cancers usually do not affect children.

Chance for passing on a variant



Genetic testing is a personal choice and your family members may choose not to have genetic testing. It is recommended that they talk with their own healthcare provider about a plan for screening.

Create a plan with your healthcare provider

These options are a guide for you and your healthcare provider. They are meant to be used along with your genetic test results and other health information. Each option may or may not be right for you. Your positive test result on its own can not predict how this condition may affect you. Please talk with your healthcare provider to make a plan that's right for you.

Options you and your healthcare provider might consider

CONDITION	RISK FOR GENERAL POPULATION	RISK FOR ATM	OPTION	MORE INFORMATION
Breast cancer	13%	17-33%	• Mammogram with consideration of tomosynthesis (3D mammogram) and consider breast MRI with contrast once per year beginning at age 40 (1)	• Helps find cancer so you can seek treatment as soon as possible. • If you have a family history of breast cancer, screening may be started 5-10 years earlier than the youngest age of breast cancer in your family.
			• There is insufficient evidence to recommend risk reducing mastectomy (surgery to remove the breasts) for all ATM-positive women at this time, however it may be considered on an individual basis, taking personal and family history into account (1)	• Helps prevent cancer.
Pancreatic cancer	2%	Increased	• There is insufficient evidence to recommend pancreatic cancer screening for all ATM-positive individuals at this time, however screening may be considered on an individual basis (1) • Individuals at higher risk due to a family history of pancreatic cancer may consider screening by MRI, MRCP (magnetic resonance cholangiopancreatography) and/or endoscopic ultrasound once per year beginning at age 50, or earlier based on family history (1). • Please see NCCN for more details on screening based on personal and family history (1)	• Helps find cancer so you can seek treatment as soon as possible • Ideally this should be done at an experienced center.
Ovarian cancer	2%	Possibly increased	• There is insufficient evidence to recommend risk reducing salpingo-oophorectomy (surgery to remove the ovaries and fallopian tubes) for all ATM-positive women at this time, but it may be considered based on your personal medical and family history (1).	• Helps prevent cancer.
Prostate cancer	12%	Possibly increased	• There is insufficient evidence to recommend earlier or more frequent prostate cancer screening among ATM-positive males at this time. However following general population recommendations for prostate cancer screening is encouraged (1). • Please see NCCN for more details on prostate cancer screening based on personal and family history (2).	

These options outline recommendations from NCCN. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Version 2.2021 (1) and Prostate Cancer Early Detection Version

2.2020 (2). © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed January 7, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. We are always learning more about genetics and disease, so please always refer to the current guidelines and recommendations when considering surveillance and treatment options. Information in this document may not include all relevant international recommendations and acts as a supplement to the Invitae result report. This information is not meant to replace a discussion with your healthcare provider and should not be considered or interpreted as medical advice.

We (and others) are here to help

Genetic counseling is recommended to help you clearly and accurately understand your results so it's important to talk to your genetic counselor or other healthcare provider about your test results. Invitae also has board-certified genetic counselors who are available to answer questions about your test results or these options. Log in to your patient portal (invitae.com) to view your results, search for a local or Invitae genetic counselor, or join Invitae's Patient Insight Network (PIN), a community where you can connect with other patients and share your experience.

Notes for personalized assessment