Welcome and Opening Overview

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Genomic Testing – Both Old and New

- Early uses of genomics were in criminal and paternity cases
- Today
  - uses of genomics are delivering material results in civil cases
  - uses and tools are growing broadly and quickly
- Much more ahead because:
  - science is racing forward with new tools
  - costs are dropping for sequencing and other forms of genomic investigation
  - continuing increases in the lists of genomically caused diseases and conditions
  - gene and cell therapy treatments – 20 are FDA approved; many more in clinical trials

https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products

Genomics and Caselaw – Older and Newer Rulings

- Harris v. Mercy Hosp., 231 Ill. App. 3d 105, 596 N.E.2d 160 (1992)(genetic testing approved in case involving alleged medical negligence)
- Bowen v. E.I. DuPont de Nemours & Co., 906 A.2d 787 (Del. 2006)(genetic testing in Benlate case – birth defects - CHARGE syndrome)
- Cruz v. Superior Court, 17 Cal. Rptr. 3d 368, 370 (Ct. App. 2004)(genetic testing in alleged medical negligence case)
- Allen v. Takeda Pharms. North America, Inc. (In re Actos® (Pioglitazone) Prods. Liab. Litig.), 2014 U.S. Dist. LEXIS 1194, 2014 WL 46818 (plaintiff prevailed in Daubert hearing involving epigenetic mechanisms for cancers to arise in less than 1 year; after ruling, $2+ billion settlement)
- Panels will provide more recent examples and articles on recent rulings

More [Cite]

Current Uses for Genomics – Categories of Cases

- Chemical product liability cases
  - Solvent cases (benzene)
  - Asbestos
- Medical malpractice cases
- Drug product liability cases
  - Actos bladder cancer cases
  - birth defect cases

[Cite]

- Environmental discharge cases
- "Bad food" cases
- Premises liability/workplace cases
  - Legionnaire's cases
  - Radiation
- Cancer cluster cases
  - site related
  - product related
- Other cases
  - Anthrax
  - Car crash injury case

[Cite]

Speakers
All Experienced in Use of Genomics in Litigation

- Solvents (benzene)
  - Howard Jarvis, Larry Chilton
  - Guzman trial – Making the Invisible Visible article
- Mesothelioma
  - Mark Zellmer
  - Kirk Hartley
- Medical and drugs
  - Dr. Thomas Morgan
  - Andrew Gendron
    - "Incomplete Penetrance" article
- ADME genes – Dr. Len van Zyl and Dr. Thomas Morgan

[Cite]

- Fundamentals of using genomics –
  - Dr. van Zyl
  - Michael Zapata
- "Environmental"
  - Adam Dinnell
  - Susan Brice
    - Use of Genetic Evience to Defend … 3 part article
  - John Kalas
- Scientific knowledge and communication
  - David Schwartz
  - Scott Horwitz - Magna Legal Services
  - Mark Zellmer
- Extended Q&A session

Articles – Use of Genomics in Litigation

- Andrew Gendron & Thomas M. Morgan, M.D., *Incomplete Penetrance: Whole-Exome Sequencing and Federal Courts,* FOR THE DEFENSE, January 2019, at 23 http://digitaleditions.walsworthprintgroup.com/publication/?m=55594&i=557674&p=24
- Mark E Zellmer, *Commentary, Toward a Defense of Mesothelioma Cases on Causation: Low Doses and Genetics*, HarrisMartin Asbestos (October 2016) (alternative version at https://www.toxictortmonitor.com/09-02-2016-toward-a-defense-of-mesothelioma-cases-on-causation/)
- Scott Elder, Anderson Kemp, Genomics in the Courtroom: The Current Landscape of DNA Technology in Criminal and Civil Litigation (IADC Jan. 19, 2021) https://www.iadclaw.org/assets/1/6/Genetic_Paper_2.pdf
- James M. Beck, *More on Genetic Testing Orders, Drug & Device Law Blog (Feb. 20, 2020) https://www.druganddevicelawblog.com/2020/02/more-on-genetic-testing-orders.html*

[Cite]

- Susan E. Brice & Dr. Whitney V. Christian, *The Use of Genetic Evidence to Defend Against Toxic Tort Claims—Part I-III,* Intell. Prop. & Tech. L.J. (2017) https://www.scribd.com/document/509142155/Brice-and-Whitney-Article-re-Uses-of-Genomics-in-Litigation
- Howard E. Jarvis, E. Paige Sensenbrenner et al, *Genetics and Genomics: Making the Invisible Visible*, FOR THE DEFENSE, April 2015, at 64 https://adamsreesepr.azureedge.net/adamsreesepr/files/uploads/documents/FTD-1504-Jarvis-Sensenbrenner-Whitmore.pdf
- Gary E. Marchant, Genetic Data in Toxic Tort Litigation, The Brief, Winter 2016 (ABA Tort, Trial & Insurance Section) https://www.scribd.com/document/415652109/Marchant-Genetics-in-Toxic-Tort-Litigation-2016
- Christine R. M. Kain & Christin Jaye Eaton, *The Double-Edged Sword: Genomic Profiling in Drug and Chemical Litigation,* Faegre Baker Daniels (2015) https://www.faegredrinker.com/en/insights/publications/2015/5/the-doubleedged-sword-genomic-profiling-in-drug-and-chemical-litigation

[Cite]

Looking Ahead – More Uses – More Genomic Tools

- Cancer clusters and medical monitoring cases
  - Genomic analyses provide ways to assess cases
- Liquid biopsy – early detection of cancers
- Real–time monitoring of antibodies and gene expression during exposure to most any substance
  - https://systemx.stanford.edu/news/2021-02-08-000000/stanford-researchers-develop-real-time-biosensor-continuous-blood

Examples of Recent Cancer Cluster Cases

- Examples of recent cancer cluster cases and medical monitoring claims
- Various site related medical monitoring cases
  - Lockheed Martin – recent denial of motion to dismiss medical monitoring claims related to alleged exposures to chemicals from Orlando area facility
    - https://www.law360.com/articles/1384717/lockheed-martin-can-t-escape-fla-contamination-suit
  - ethylene oxide cases – various current and former facilities

- "**MILLIE CORDER DIDN'T** know why there was so much cancer in her family. Her daughter, Cheryl, was only 27 when she was diagnosed with breast cancer and 34 when the disease killed her in 2002. By that time, Millie's husband, Chuck, had been diagnosed with prostate cancer. He recovered, only to develop skin cancer in 2005. The next year, Millie herself was diagnosed with colon cancer and, two years after that, with breast cancer. Those years were a blur as she shuttled back and forth between her office, her home, and doctors' appointments. While she was recovering, Chuck died of his cancer. Two years later, her stepson, Brian, was diagnosed with and died from lung cancer. (emphasis added)
  - https://theintercept.com/2021/03/18/epa-pollution-cancer-ethylene-oxide/

- see ToxicoGenomica White Paper and slides from Perrin conference on Young Mesothelioma Cases

More Looking Ahead – Somatic Signature Mutation Patterns

- Somatic signature mutation patterns for particular toxins
  - patterns exist in some tumors
  - dozens of chemicals investigated
  - signature somatic mutation patterns for smoking-induced cancers are prime examples
  - costs to find signature patterns in tumors are falling
  - see slides from Perrin Settlement Structures conference

Conference Instructions

- **Triggering Panels**: After each panel, a "call to action" button will pop up asking you to click to move to the next panel.
- You also can go to the next panel by going back to the main conference page and then clicking on the panel.

- **CLE**: If you are seeking CLE credit, please answer the polling question that will pop up on your screen during the presentations. [Perrin team will do one polling question for each panel]
- If you are seeking CLE, please provide your state and license number so that Perrin team may apply for CLE on your behalf for each panel.

- **CLE- Evaluations**: Please fill out the evaluation form for each panel.

PANEL 1 SLIDES

Results from Genetic Sequencing in Mesothelioma Cases

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Mesothelioma Cases
Overview of Orders on Whole Genome Sequencing

- Difficult to track genetic testing rulings because
  - Mealey's and HarrisMartin only occasionally pick up motions to compel and results
    - E.g. Holsten case in Madison County, Cowger case in Chicago
  - No motion papers for agreed orders

- 3 mesothelioma case resulted in court approval or agreements for whole genome sequencing (WGS)
  - either by order after defense motion to compel or agreement between counsel
  - cases in state court in IL (Madison County), MO, TN
  - all cases resolved after WGS performed

- At year end 2020, WGS denied in Cook County case (Cowger)
  - case is ongoing and may result in trial and then appeal of denial of WGS
  - plaintiff's sole expert recently published new data contrary to his testimony

Overview - Results of WGS in 3 Mesothelioma Cases

- Cole – Missouri state court
  - agreed order entered (Baron & Budd for plaintiff)
  - extensive germline mutations found in cancer associated genes; case resolved
  - results disclosed in expert deposition

- Holsten – Madison County
  - testing proceeded by agreement after motion to compel filed (Maune Raichle for plaintiff)
  - extensive germline mutations found in cancer associated genes; case resolved
  - results not yet published

- Bailey – Tennessee state court
  - order entered after motion to compel filed (Nichol and Shrader firms for plaintiff)
  - extensive germline mutations found in cancer associated genes; case resolved
  - results not yet published

- [Cite]

Cole Case – Overview

- Cole case
  - extensive germline mutations found in cancer associated genes
- Overall opinion of Dr. van Zyl:
  - Mr. Cole's genome harbored a broad set of pathogenic germline mutations in cancer associated genes, which caused his pleural mesothelioma at age 36, regardless of any exposure to asbestos
- [Cite]

Cole – Personal and Family Medical Histories

- Mr. Cole's personal cancer and phenotypes history included "red flags" suggesting genetic causation
  - pleural mesothelioma at age 36
  - tumors/neoplasms early in life (e.g., a benign lentiginous compound melanocytic nevus neoplasm/lesion at age 29)
  - other possibly genetic phenotypes

- Mr. Cole's family cancer history
  - 2 relatives developed cancers, including a leukemia in maternal grandmother
  - other possibly genetic phenotypes

- [Cite]

Overview – Some of Mr. Cole's Germline Mutations in Cancer Associated Genes

- Multiple germline variants identified in broad set of > 15 cancer associated genes
  - multiple germline mutations in some genes
  - some homozygous mutations (means identical in both genes (alleles))

- Multiple germline variants in genes known KMT2C, MLH1, and PMS2, as well as MSH2, EPCAM, NOTCH 2, 3 & 4.

- Additional, adverse germline homozygous and heterozygous variants identified in ALK, APC, ATM, BRCA1 & 2, EXO1, FANCA, FLT3, NF1, PALB2, RECQL4, WRN and XPC.

- [Cite]

Germline Mutations in Mr. Cole Caused 1) Excessive Endogenous Somatic Mutations and 2) Impaired Repair of Endogenous Somatic Mutations

- Germline mutations caused failures in two critical cellular systems of Mr. Cole
- 1) pathogenic germline mutations caused Mr. Cole's body to generate vastly increased numbers of "endogenous somatic mutations"
  - endogenous somatic mutations can drive cancers and/or provide a "second hit" to the genome, regardless of any exposure to asbestos or other substances
- 2) germline mutations also caused failure of genome to repair endogenous somatic mutations
- Overall, virtually every cell in Mr. Cole was catastrophically mutated, and so skin lesions, tumors and cancers were going to occur, regardless of any exposure
- [Cite]

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Findings of Germline Mutations in *KMT2C* Gene

Table 1: *KMT2C* variants in Mr. Cole's non-cancerous germline DNA

Gene	Variant	Type	AA change	Zygosity
KMT2C	rs147851738	missense	N2830H	Heterozygous
KMT2C	rs28522267	missense	C988F	Homozygous
KMT2C	rs150073007	stop gained, frameshift	Y816X	Heterozygous
KMT2C	rs10454320	missense	T316S	Heterozygous

- *KMT2C* mutations are reported in the scientific literature to cause both blood cancers and mesotheliomas
  - further specifics follow

- [Cite]

Overview of Adverse Impacts of Mr. Cole's 3 Germline Variants in *KMT2C*

- Mr. Cole's three pathogenic *KMT2C* variants have been shown in the medical literature to:

- (a) exponentially increase endogenous somatic mutations
- (b) independently drive initiation of both leukemia and malignant mesothelioma tumorigenesis
- (c) initiate DNA double-strand breaks (DSBs)
- (d) initiate chromosomal translocations
- (e) dysregulate normal tissue specific gene expression via DNA enhancers, initiating tumorigenesis
- (f) specifically downregulate/activate expression of tumor suppressor genes (*i.e.*, *p53* and *p73*) / oncogenes, respectively
- (g) disrupt normal epithelial differentiation and promote malignant migratory phenotypes through epithelial-to-mesenchymal transition (EMT)

- [Cite]

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KMT2C Germline Variant #1 and Literature

- The first high risk pathogenic (disease causing) variant identified in Mr. Cole's genomic DNA completely abrogates the function of the protein. The mutation was a heterozygous *KMT2C* p.Y816X gene variant (rs150073007). This p.Y816X variant was initially published as an inherited, highly penetrant, inactivating pathogenic mutation that predispose individuals to Familial Nasopharyngeal Carcinoma (Sasaki *et al.*, 2015). The mutation introduces a stop codon at position 816 near the N-terminus of the protein, which.
  - Sasaki MM, Skol AD, Bao R, et al. Integrated genomic analysis suggests MLL3 [KMT2C] is a novel candidate susceptibility gene for familial nasopharyngeal carcinoma. *Cancer Epidemiol Biomarkers Prev*. 2015;24(8):1222-1228.

- This exact same germline variant was recently identified as a mesothelioma causing, high risk mutation in a family with a high prevalence of familial (hereditary) mesothelioma. The authors also noted that members of this family, with its high prevalence of familial mesothelioma, were all negative for germline BAP1 mutations, further confirming the existence of other predisposing causal genetic factors such as *KMT2C* gene mutations.
  - Hylebos M, Op de Beeck K, van den Ende J, et al. Molecular analysis of an asbestos-exposed Belgian family with a high prevalence of mesothelioma. *Fam Cancer*. 2018;17(4):569-576.

- This family also shared another feature with Mr. Cole: both had closely related family members with hematological neoplasms.

KMT2C Germline Variant #2 and Literature

- Mr. Cole also was heterozygous for a second, very rare pathogenic missense *KMT2C* variant (rs10454320; p.T316S).

- This variant was previously identified as a familial deleterious germline mutation that replaces threonine with serine at amino acid 316 (Sasaki *et al.*, 2015). The COSMIC database lists this as a pathogenic variant (https://cancer.sanger.ac.uk/cosmic/mutation/overview?id=4162024).

- Based on the striking findings of multiple, extremely rare deleterious germline mutations in the *KMT2C* gene, Sasaki and colleagues (2015) concluded: "Taken together, the finding of familial mutations predicted to abolish [*KMT2C*] function in two unrelated families with multiple cancer-affected members lead us to the intriguing hypothesis that inactivating mutations of [*KMT2C*] may be associated with a highly penetrant and previously unsuspected cancer-predisposition syndrome" (Sasaki *et al.*, 2015).

  - Note: some articles refer to *KMT2C* as *MLL3*

- [Cite]

KMT2C Germline Variant #3 and Literature

- A third, extremely rare homozygous missense *KMT2C* variant was found to be present in both of Mr. Cole's copies of the gene, which significantly increases the biological impact of the mutation. The mutation,(rs28522267; p.C988F) is listed as pathogenic in the COSMIC database (https://cancer.sanger.ac.uk/cosmic/mutation/overview?id=150426

- Located in the highly conserved Plant Homeodomain finger (PHD) functional domain, this mutation has been shown to abrogate *KMT2C* protein function (Patil et al., 2015). This variant was recently reported to occur in childhood tumor patient-derived xenograft models (Rokita *et al*., 2019).
  - Rokita JL, Rathi KS, Cardenas MF, et al. Genomic Profiling of Childhood Tumor Patient-Derived Xenograft Models to Enable Rational Clinical Trial Design. *Cell Rep*. 2019;29(6):1675-1689.e9. doi:10.1016/j.celrep.2019.09.071

- Further evidence of carcinogenicity arises from Wang and colleagues (2018) mutating the *KMT2C* Plant Homeodomain finger. The mutation prevented the KMT2C protein from associating with the BAP1 protein.
- Their findings suggest that an important function of *BAP1* protein is to regulate KMT2C activity, and that mutations in the highly conserved KMT2C PHD functional domain abrogate its interactions with the KMT2C PHD-BAP1 tumor suppressor complex, affecting H3K4me1 levels and enhancer activity, promoting cancer (Wang *et al*., 2018).
  - Wang L, Zhao Z, Ozark PA, et al. Resetting the epigenetic balance of Polycomb and COMPASS function at enhancers for cancer therapy. *Nat Med*. 2018;24(6):758-769

- [Cite]

Big Picture Lessons from Whole Genome Sequencing in Cole Case

- Whole genome sequencing produces far more objective data and best possible evidence
  - testing for a few genes was once logical because of cost constraints, but now is illogical and denies access to the best possible evidence of causation

- There is no "fishing expedition" when the objective genetic "red flag" criteria are present
  - existing criteria are conservative – more expansive criteria continue to be put in place, over time

- Illogical and unfair to demand moving party predict germline mutations to be tested/found

  - No one could have predicted the 3 specific, pathogenic germline mutations in *KMT2C* gene
  - No one could have predicted overall combination of pathogenic mutations in Mr. Cole

- Refusal to permit whole genome sequencing raises major legal issues regarding differential etiology and inferences when objective genetic red flags are present

- [Cite]

ToxicoGenomica

Cowger - WGS Denied – Flawed Decision

- Cowger – WGS denied in ruling at year end 2020
- Plaintiff had stipulated to BAP1 testing (Weitz Luxenberg and Cooney and Conway for plaintiffs)
- Ruling based on Frye standard that requires "general scientific acceptance," as compared to more expansive Daubert standard, and some other state's versions of Frye standard
- Case is ongoing
  - trial logically will produce differential etiology issues regarding absence of whole genome sequencing, especially in view of myriad "red flags" in personal and family medical histories
  - possible appeal of issue regarding whole genome sequencing
- [Cite]

Big Pictures Flaws in Cowger Case Process and Orders

- In 2020, trial judge refused to require production of complete medical records
  - defendant had supported request with testimony from physician with genetic expertise
  - physician pointed out "red flags" known as of that stage of case

- Preliminary *Frye* hearing orders, and ultimate ruling, quoted and accepted plaintiff's mis-framing of scientific and legal issues;
  - according to plaintiff, issue was whether a single germline mutation of BAP1 gene could cause a mesothelioma
  - defendant argued for whole genome sequencing in order to be able to see all germline mutations; many genes are known to be involved in mesotheliomas

- During *Frye* hearing, trial court erroneously declined some evidence offered by defense, stating that personal and familial medical histories were not relevant to *Frye* issue
- e [Cite]

Frye Error on *BAP1* Haploinsufficiency

- Cowger court also committed a *Frye* error with respect to haploinsufficiency and the *BAP1* gene
- Specifically, the following quote from 5 page of the order shows the trial court deferring to idiosyncratic views and experiences of Dr. Testa, with no explanation for disregarding numerous peer reviewed articles stating that BAP1 gene can and does act in a haploinsufficent manner
- "Additionally, while Dr. van Zyl may be of the mind that a BAP1 germline mutation can operate in a haploinsufficient manner (i.e., "meaning that deletion of one allele [...] is sufficient to cause cancer"), it is the opinion of Dr. Testa that "this idea of haploinsufficiency" is not widely accepted within the scientific community. (Id., at pp. 4-5 (citing V. 58-59) (quoting T. 81)).

- [Cite]

Defense Submitted Peer Reviewed Articles on *BAP1* Haploinsufficiency

- Image below was defendant's slide 27, which lists peer reviewed articles stating BAP1 haploinsuffiency; all hearing slides were admitted into evidence

The Scientific Literature Shows that *BAP1* is a Haploinsufficient Gene

- "A pathogenic variant in one BAP1 allele results in **haploinsufficiency of BAP1**, a tumor suppressor protein." Pilarski, et al. (2016); (updated 2020).
- "**BAP1 haploinsufficiency** was characterized by a distinct expression profile including genes related to chromatin remodeling, DNA repair, and activation of immune checkpoint receptors, a pattern associated with the inflammatory TME." Carbone, et al. (2020).
- "**BAP1 is a haploinsufficient tumor suppressor**..." Perkail, et al. (2020).
- "Our novel contribution to PeM (Malignant peritoneal mesothelioma) is that we provide evidence from integrative multi-omics analyses that **BAP1 haploinsufficiency** (BAP1del) forms a distinct molecular subtype of PeM." Shrestha (2019).
- "Deletion of Bap1 alone in the thoracic cavity in a cohort of 20 mice did not result in mesothelioma during the lifetime of the mice (monitored for up to 700 d*)* **except in one heterozygous floxed mouse** . . ." "Heterozygous deletion of Bap1 in either NC or NCa mice showed significant tumor acceleration without evidence of loss of heterozygosity (LOH) in the tumors, indicative of a dose dependent effect of Bap1 on tumor development . . ." Badhai, et al. (2020).
- "Therefore, it is of great importance to verify all mutations predicted to have an impact on BAP1 functions, because of their possible **dominant-negative** action in the presence of one copy of the BAP1 wild-type (WT) allele. Indeed, several

Key *Frye* Error on Frequency and Use of Whole Genome Sequencing

- According to the Court's opinion at 5, quoting plaintiff's expert, Dr. Joseph Testa:
  - "it should come as no surprise that the ""sequencing of person's whole genome "hasn't even been done in research, [as it would go] way beyond the pale."" (See Exhibit A, at p. 3 (citing T. 74) (quoting T. 187) (emphasis omitted)).

- In fact, however, the defendant submitted an extensive record of peer reviewed medical articles which showed:
  - thousands of whole genome sequences have been created and analyzed in research, and
  - tens of thousands of additional whole genome sequences are planned for and in progress in national health research programs

- Trial court did not address extensive record of peer reviewed articles

- [Cite]

Recent Study by Dr. Testa Contradicts His Testimony in Cowger Hearing

- The Cowger trial court's finding that whole genome sequencing is "beyond the pale" is further undercut by a recent study involving Dr. Testa
- Dr. Testa and colleagues very recently published a scientific poster and paper summarizing the results of a study based on whole genome sequencing of 14 people with mesothelioma
  - Poster published May 7-9, 2021 as part of virtual, biannual meeting of physicians and researchers focused on mesothelioma (iMig 2021)
  - Uncorrected draft of article published online on May 18
  - Listed authors include Dr. Testa, multiple members of his Fox Chase lab team, two doctors in Italy, and Dr. Jill Ohar, a Wake Forest physician occasionally called to testify by mesothelioma plaintiffs
- [Cite]

May 2021 Poster by Dr. Testa Regarding Study of 14 Whole Genome Sequences of Persons with Mesothelioma

FOX CHASE CANCER CENTER
TEMPLE HEALTH

Rare, Non-BAP1-Related Potential Tumor Predisposition Gene Variants in Families with Mesothelioma and Other Cancers Identified Using Whole Genome Sequencing

Mitchell Cheung [1], Yuwaraj Kadariya [1], Eleonora Sementino [1], Ilaria Cozzi [3], Valeria Ascoli [3], Michael J. Hall [4], Jill A. Ohar [2], and Joseph R. Testa [1]

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ABSTRACT

There is irrefutable evidence that germline BAP1 mutations can contribute to malignant mesothelioma (MM) susceptibility. However, BAP1 mutations are not found in all cases with evidence of familial MM or in other high-risk cancer families affected by various cancers, including MM. The goal of this study was to use whole genome sequencing (WGS) to determine the frequency and types of germline gene variants occurring in 12 MM patients selected from a series of 141 asbestos-exposed MM patients with a family history of cancer but without a germline BAP1 mutation. WGS was also performed on 2 MM cases, a proband and sibling, from a previously reported family with multiple cases of MM without inheritance of a predisposing BAP1 mutation. Altogether, germline DNA sequencing variants were identified in approximately 20 candidate cancer-related genes in 10 of the 13 probands. The germline mutations consisted of indel (predicted frameshift), splice site, and missense mutations. In addition, structural variation detection software programs were used to discover large germline deletions in two genes, which could have been overlooked using standard mutation analysis and/or exome sequencing. Among the 13 MM index cases, 6 exhibited one or more predicted pathogenic mutations; 2 of these same 6 cases also had either a deletion encompassing multiple exons of a gene or an entire gene. Affected genes encode proteins involved in DNA repair (ATM, ATR, BRCA2, BRIP1, CHEK2, MLH3, MUTYH, POLE, POLE4, POLQ, XRCC1), chromatin modification (ARID1B, DNMT3A, JARID2, SETD1B) or other cellular pathways: MSH4. Notably, POLQ, and CHEK2 were found to be mutated in more than one proband and occasionally mutated/deleted somatically in MM tumors in The Cancer Genome Atlas database. Collectively, the findings suggest that, in addition to BAP1, germline mutations of other genes may occasionally contribute to MM susceptibility.

BACKGROUND

MM is a highly aggressive malignancy that arises from the serosal lining of the pleural, peritoneal, and pericardial cavities. Epidemiological studies have established that exposure to asbestos fibers is the primary cause of MM. In the USA, ~3,200 cases of MM are diagnosed annually, and the incidence of this disease is expected to increase over the next two decades due to past occupational exposure to asbestos. MM is characterized by a long latency, typically 20-40 years, from the time of exposure to asbestos to diagnosis.

Recently, germline mutations of the *BAP1* tumor suppressor gene were reported in families with multiple MMs, benign melanocytic tumors, uveal/cutaneous melanomas, kidney and basal cell carcinomas, and meningiomas. We reported *in vivo* genetic evidence that various germline heterozygous mutations of mouse *Bap1* accelerates the development of asbestos-induced MM. Only 2/93 spontaneous MMs were seen in unexposed *Bap1*-mutant mice, indicating that high penetrance of MM requires environmental exposure to asbestos or other carcinogenic mineral fibers. Despite the identification of germline mutations in *BAP1* as predisposing to familial MM, there are a number reports indicating that the gene may not be involved in all familial cases. In our analysis of 150 MM patients with a strong family cancer history, we discovered germline *BAP1* mutations in 9 (6%) individuals. In another study, we discovered an Italian family with multiple cases of MM but no germline *BAP1* mutation. Therefore, in this investigation, we utilized NGS to identify germline mutations that may predispose to familial MM in a set of patients lacking germline *BAP1* mutations.

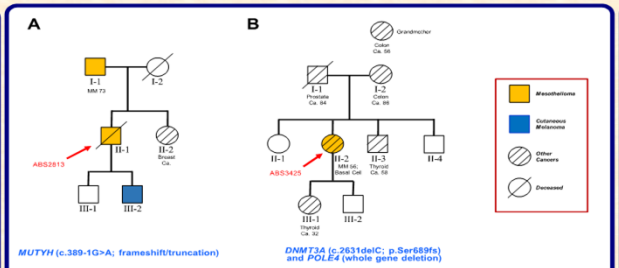


Fig. 1. Pedigrees of two unrelated MM patients without germline *BAP1* mutations. A) Pedigree showing proband (arrow) with pleural MM as well as additional cancers in the son (III-2, cutaneous melanoma), sibling (II-2, Breast Ca.) and father (I-1, MM). B) Pedigree showing proband (arrow) with both peritoneal MM and basal cell carcinoma. Thyroid cancer was diagnosed in her daughter (III-1) and the sibling (II-3). There are also relatives with colon ca. (mother and grandmother).

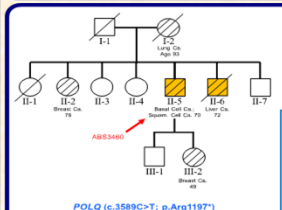


Table 1. Pathogenic non-*BAP1*-related germline variants in MM patients from high-risk cancer families

No. Probands	Probands with pathogenic variants*	Probands with missense variants	Probands without significant variants
13	6 (46%)	4	3

**indels, splice site mutations, nonsense mutations, deletions*

Fig. 2. Family pedigree of patient ABS3460, who has had both pleural and peritoneal epithelioid MM as well as basal cell carcinoma and squamous cell carcinoma. The proband had a brother who had MM and liver cancer, and there have been several other carcinomas in this family. The proband has a germline inactivating mutations in both *POLQ* and *XRCC1*, as well as missense mutations in *SETD1B* (c.2554C>T; p.Arg852Cys) and *ARID1B* (c.2405C>T; p.Ser802Leu) not predicted to be pathogenic.

Table 2. Candidate genes with germline mutations identified by WGS

Symbol	Gene	Function	Mutation
APC	APC regulator of WNT signaling pathway	Tumor suppressor that antagonizes the Wnt signaling pathway	Missense
ARID1B	AT-Rich Interaction Domain 1B	Component of the SWI/SNF chromatin remodeling complex in cell cycle activation	Missense
ATM	ATM Serine/Threonine Kinase	Double strand break DNA damage sensor	Missense
ATR	ATR Serine/Threonine Kinase	Single strand break DNA damage sensor	Missense
BRCA2	BRCA2 DNA repair associated	Homologous recombination mediated repair of double-strand DNA breaks	Indel
BRIP1	BRCA1 interacting protein C-terminal helicase 1	Member of RecQ DEAH helicase family that complexes with BRCA1 for normal double strand break DNA repair	Missense
CBFA2T3	CBFA2/RUNX1 translocation partner 3	Transcription factor binding protein that facilitates co-repressor recruitment	Missense
CHEK2	Checkpoint Kinase 2	Blocks cell cycle progression in response to DNA damage; linked to ked with Li-Fraumeni syndrome and confers a predisposition to sarcomas, breast cancer, and brain tumors	Missense Large del.
DACT2	Dishevelled binding antagonist of beta catenin 2	Tumor suppressor inhibiting Wnt/β-catenin pathway	Missense
DNMT3A	DNA methyltransferase 3 alpha	CpG DNA methylation; interacts with EZH2, a histone methyltransferase	Indel
JARID2	Jumonji And AT-Rich Interaction Domain Containing 2	DNA binding protein that complexes with PRC2 to repress transcription	Missense
MLH3	MutL homolog 3	Repair of DNA mismatches	Missense
MSH4	MutS protein homolog 4	Meiotic homologous recombination	Indel
MUTYH	MutY DNA glycosylase	DNA glycosylase involved in oxidative DNA damage repair	Splice site
POLE	DNA polymerase epsilon, catalytic subunit	Involved in DNA repair; missense germline mutation causes colorectal polyposis	Missense
POLE4	DNA polymerase epsilon subunit 4	Accessory component of the DNA polymerase epsilon complex	Gene del.
POLQ	DNA polymerase theta	Mediates microhomology-mediated end-joining repair of double strand DNA breaks	Nonsense Missense
RHBDF2	Rhomboid 5 homolog 2	Regulates secretion of several EGFR ligands; activating germline mutations causes esophageal cancer and hyperkeratotic skin lesions	Missense
SETD1B	SET domain containing 1B	Histone H3 K4 trimethylation (active transcription)	Missense
SMARCB1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1	Subunit of SWI/SNF chromatin remodeling complex	Indel
XRCC1	X-Ray Repair Cross Complementing 1	Repair of DNA single-strand breaks through base excision repair	Indel

CONCLUSIONS

- Germline mutations in ~20 promising candidate genes were identified in 10 of 13 *BAP1* mutation-negative families.
- Candidate genes encoded proteins involved in critical cellular functions, particularly DNA damage repair and chromatin modification.

ACKNOWLEDGMENTS: [1]Work supported by a grant from the Mesothelioma Applied Research Foundation (J. A. Ohar), NCI grants CA175691 (J.R. Testa and F.J. Rauscher) and CA06927 (Fox Chase Cancer Center), NIEHS grant P42 ES023720 (UPenn Superfund Research and Training Program Center), an appropriation from the Commonwealth of Pennsylvania, and a gift from the Local #14 Mesothelioma Fund of the International Association of Heat and Frost Insulators & Allied Workers.

Paper by Dr. Testa et al Regarding 14 Whole Mesothelioma Genomes

- Paper published after poster - May 18, 2021 - Cheung M, Kadariya Y, Sementino E, et al. *Novel LRRK2 mutations and other rare, non-BAP1-related candidate tumor predisposition gene variants in high-risk cancer families with mesothelioma and other tumors* [published online ahead of print, 2021 May 18]. *Hum Mol Genet*. 2021; ddab138 (uncorrected manuscript)
- Article abstract includes the following statements:
  - "The goal of this study was to use whole genome sequencing (WGS) to determine the frequency and types of germline gene variants occurring in 12 MM patients selected from a series of 141 asbestos-exposed MM patients with a family history of cancer but without a germline BAP1 mutation, [and two other selected persons with mesothelioma]."
- Contrast those statements with Dr. Testa's testimony and the trial court's conclusion that:
  - "it should come as no surprise that the ""sequencing of person's whole genome "hasn't even been done in research, [as it would go] way beyond the pale.""

- [Cite]

Paper by Dr. Testa et al Regarding 14 Whole Mesothelioma Genomes

- Article abstract also includes the following statements:
- "… expression of LRRK2 was undetectable or downregulated in a majority of primary MMs and MM cell lines we examined, implying that loss of LRRK2 expression is a newly recognized tumor suppressor alteration in MM."
- "Altogether, germline DNA sequencing variants were identified in 20 cancer-related genes in 10 of the 13 probands"
- "Affected genes encode proteins involved in DNA repair (ATM, ATR, BRCA2, BRIP1, CHEK2, MLH3, MUTYH, POLE, POLE4, POLQ, XRCC1), chromatin modification (ARID1B, DNMT3A, JARID2, SETD1B) or other cellular pathways: LRRK2 (2 cases) and MSH4."
- [Cite]

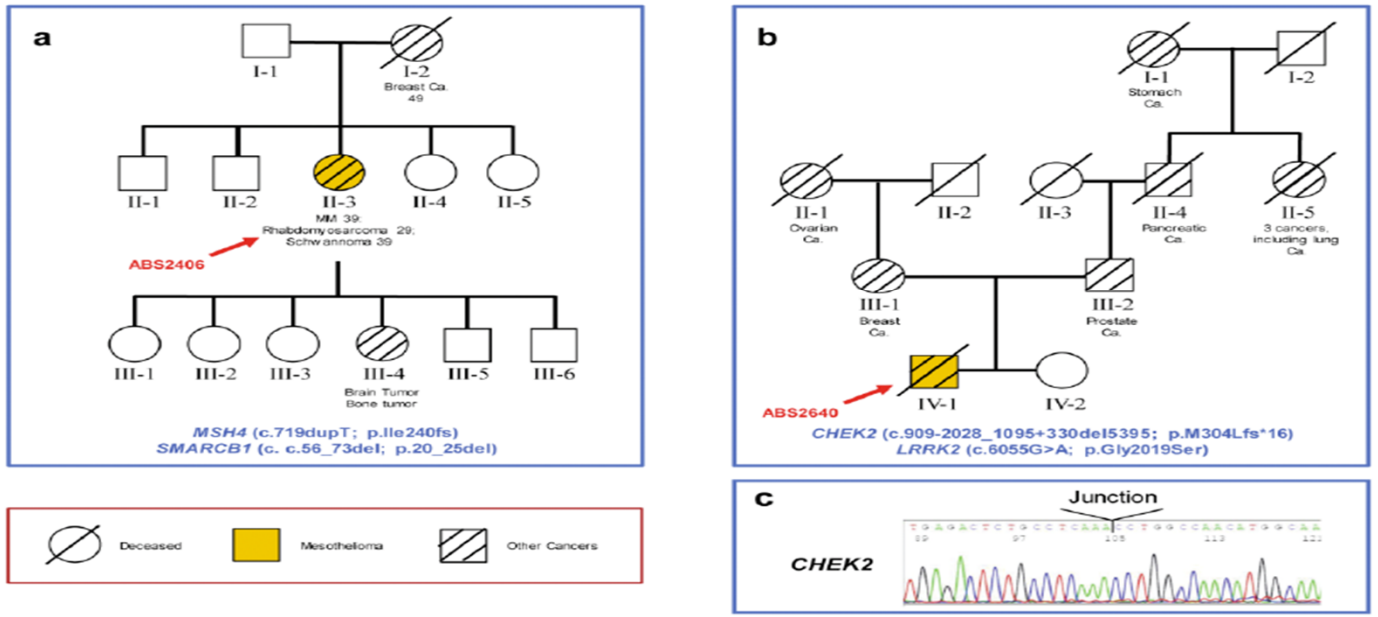
Family Cancer History - Quotes from Testa et al Paper

- Paper includes statements illustrating the importance of looking at all cancers in a family
- "These 12 MM cases were selected from families having a high overall incidence of cancer generally, not necessarily a personal or family history strongly indicative of BAP1- [Tumor Predisposition Syndrome] TPDS."
- "In addition, WGS was also performed on two additional MM cases from the Italian family that lacked a germline BAP1 mutation (20)."
- Note: researchers eschewed conservative view of pertinent cancers in family history
- [Cite]

Diversity of Cancers in Family Cancer Histories – Testa Figure 1

- Paper includes statements illustrating importance of looking at all cancers in family history
- Figure 1 shows family pedigrees, with some ages of onset and broad range of cancers identified
  - breast, stomach, colon, prostate, pancreatic, lung, ovarian, rhabdomyosarcoma, schwannoma, brain tumor, bone

Fig. 1



- [Cite]

Diversity of Germline Mutations and Cancers – More Testa Figure 1

- Remainder of Figure 1 provides some further specifics on diversity of germline mutations and cancers in three of the families stricken by cancers

Figure 1. Pedigrees of three families in which a proband (arrows) with malignant mesothelioma (MM) has a predicted pathogenic germline mutation. **a**) Family of patient ABS2406, who was found to have an indel mutation involving *MSH4* (c.719dupT; p.Ile240fs). In addition to MM, this proband had a rhabdomyosarcoma and a Schwannoma. **b**) Family of MM patient ABS2640m who had a 5395-bp deletion of *CHEK2* exons 9 and 10 (c.909-2028_1095+330del5395; p.M304Lfs*16) was predicted by several WGS structural variation analysis programs and confirmed by Sanger sequencing of a PCR product encompassing the junction created by the deletion (**c**). This individual also had a germline pathogenic kinase-activating mutation of *LRRK2* (c.6055G>A; p.Gly2019Ser).

- [Cite]

Found Multiple Combinations of Germline Mutations - Quotes from Testa et al

- At 7, paper illustrates the presence of combinations of germline mutations
- "In several MM cases, 3 or 4 candidate tumor susceptibility gene variants were identified in the same individual"
- Contrast that finding of multiple germline mutations in multiple genes to the focus on only one allele of one gene by Mrs. Cowger's counsel and the trial court
- [Cite]

LRRK2 Gene - Quotes from Testa et al

- At 16, paper refers to *LRRK2* gene as involved in multiple cancer and non-cancer phenotypes, including Parkinson's disease

- "Ten different pathogenic missense mutations in this gene [*LRRK2*] have been described in Parkinson disease (52), and germline *LRRK2* G2019S missense mutations have been found in ~10% of individuals with Parkinson's disease (53)."
- "Interestingly, epidemiological studies have indicated that *LRRK2* G2019S carriers have an increased risk of developing cancer, including hormone-related neoplasms (prostate and breast carcinomas), colon and kidney carcinomas, as well as meningioma (53), the latter two also part of the BAP1-TPDS tumor spectrum (11-13)."
- [Cite]

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- [Cite]

Exome Sequencing Can Miss Mutations - Quotes from Testa et al

- At 17, researchers explicitly pointed out that whole genome sequencing is valuable because more limited sequencing (e.g. exome sequencing) can fail to find adverse structural variants in genes:
- "The utilization of structural variation detection programs such as Manta and Delly has allowed us to identify large scale deletions of the CHEK2 and POLE4 genes from WGS data.
- "These alterations would have been highly unlikely to be discovered if exome sequencing was performed instead of WGS or if only standard mutation detection programs were used to analyze WGS data."
- "The deletion that encompasses POLE4 has not been reported yet to the best of our knowledge, and the incidence and its association with disease susceptibility may be of significant."
- [Cite]

More to Be Gleaned from Testa 14 Whole Genomes Study

- Other notable findings are in the paper and supplemental materials, but cannot be briefly summarized here
- Of course, deposition and document discovery of Dr. Testa and colleagues has not yet occurred regarding the 14 whole genomes study
- Discovery should reveal:
  - when the study was conceived, performed and analyzed, and how those dates relate to Dr. Testa's testimony in Cowger
  - the complete results of WGS sequencing results for each genome
  - whether claimed asbestos exposure histories were carefully investigated by persons actually knowledgeable regarding exposures

- [Cite]

Outcomes on Merits of Sequencing in Mesothelioma Cases

- 15 known rulings on merits of requests/motions for genetic sequencing in mesothelioma cases
  - Chart available on request to khartley@lspgrp.com
- Broad range of defense firms have made requests/filed motions for genetic sequencing
- Various national or local plaintiff firms have:
  - 1) opposed and lost on the merits of motions to compel some form of genetic sequencing, and/or
  - 2) agreed to some form of sequencing
    - Baron and Budd (Cole)
    - Kazan McClain (Ortwein)
    - Maune Raichle (Holsten)
    - Nichol (Bailey)
    - Simmons Hanly Conroy (Wassinger)
    - Shrader (Bailey)
    - SWMK (Bergstrom)
    - Weitz Luxenberg (Figueroa, Mandel, Lanzo, Thrash)
- [Cite]

ToxicoGenomica

More on Outcomes on Merits of Sequencing In Mesothelioma Cases

- Some plaintiff firms have succeeded on the merits in opposing state court motions to compel some form of genetic sequencing (excludes rulings where defendant filed motion too late or invoked wrong process)
  - Weitz Luxenberg, Cooney & Conway (Cowger)
  - Kazan McClain (Marshall, Reyes – both in Alameda County)

- Federal court in California applied California law and granted defense motion to compel genetic sequencing (Thrash)

- Various motions and orders pertain only to sequencing of BAP1 or TP53 genes

- [Cite]

Mechanisms to Manage Concerns About Whole Genome Sequencing

- Some judges have expressed concerns that use of whole genome sequencing may needlessly reveal that a person or family carries a genetic trait that is highly adverse (e.g. a highly adverse gene mutation for Alzheimer's or Parkinson's)

- This "dread gene" concern can be readily managed in multiple ways:

  - in a case where the issue is cancer causation, parties can agree or court can order experts not to report on genes not involved with cancer

  - require the parties to mediate more complex concerns before a neutral expert in genetic counseling or other pertinent aspects of genetics

- [Cite]

Parties and Courts Should Accept Publication of Data Gathered in Cases

- Peer reviewed scientific literature includes thousands of "case reports" that describe medical findings and events related to a particular patient, with the report typically anonymized

- Well done case reports can offer useful insights or raise new questions to be addressed
  - Jackevicius C. The Value of Case Reports. *Can J Hosp Pharm*. 2018;71(6):345-346. ("Despite their subservience to randomized controlled trials in the evidence hierarchy, well-written case reports and case series play an important role in evidence generation and in clinical practice.)

- Accordingly, from a scientific progress perspective, parties and courts should accept reports on the results of data generated in litigation, including sequencing data

- First Amendment and due process rights also exist, for both plaintiffs and defendants, who may wish to publicize that results of genomic testing in litigation are not (or are) showing a relationship between a gene and an environmental event or exposure

- [Cite]

Examples of Publication of Data Gathered in Mesothelioma Litigation

- Drs. Kradin and Moline are both expert witnesses frequently called by plaintiffs to testify in mesothelioma cases
- Both have published medical journal articles with data drawn from mesothelioma litigation files
  - Shih AR, Kradin RL. Malignant mesothelioma in Lynch syndrome: A report of two cases and a review of the literature. *Am J Ind Med*. 2019;62(5):448-452.
  - Moline J, Bevilacqua K, Alexandri M, Gordon RE. Mesothelioma Associated With the Use of Cosmetic Talc. *J Occup Environ Med*. 2020;62(1):11-17
- At 18, Testa et al paper refers to selection of families to study using information drawn from data generated in mesothelioma litigation
  - "Twelve U.S. or Canadian cases of MM were from a series of 141 MM patients with a family history of cancer but with no germline mutation of *BAP1* (18). All 12 cases had a known history of asbestos exposure and were identified via one or more of the following: … "3) independent medical evaluations for medical-legal purposes."
- [Cite]

Examples of Opinions Naming Persons and Genetic Issues or Mutations

- Published opinions and orders of courts commonly identify plaintiffs, family members and possibly genetic conditions at issue, including trial court orders published in specialty journals focused on subsets of litigation

- Mesothelioma case examples include opinions/orders on genetic testing in Bergstrom, Cowger, Ortwein, Reyes, and Thrash

- Examples of appellate and federal district court opinions include
  - Bowen v. E.I. DuPont de Nemours & Co., 906 A.2d 787 (Del. 2006)
  - Burt v. Winona Health, 2018 U.S. Dist. LEXIS 128944, 2018 WL 3647230 (D. Minn.)
  - Kirk v. Schaeffler Group USA, Inc., 2014 U.S. Dist. LEXIS 83963, 2014 WL 2807681 (W. D. Mo.)
  - Williams v. Quest Diagnostics, Inc., 353 F. Supp. 3d 432 (D.S.C. 2018)

- [Cite]

Overall Results – Genetic Testing

- **WGS in "Benzene" Cases:** In benzene cases, whole genome or whole exome sequencing has been repeatedly approved by courts or agreed to by parties

- **WGS in Mesothelioma Cases**: In mesothelioma cases, whole genome sequencing has approved by a court or agreed to by counsel in 3 mesothelioma cases where defense had support from experts in genetics
  - WGS denied in one case still in progress, with new evidence still emerging

- **Single Gene Testing**: Not aware of any single gene testing in "benzene" cases. Testing of a single gene has been implemented in some mesothelioma cases, but is materially less informative than whole genome sequencing

- [Cite]

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Overall Results – Genetic Testing

- **Combinations of Germline Mutations**: Whole genome sequencing often will provide objective, quantitative data showing multiple, pathogenic germline mutations that a defendant may argue were the cause of the cancer at issue in "benzene" or mesothelioma cases

- **"Red Flags"**: Combinations of pathogenic germline mutations are especially likely to be present in people with little or no known exposures, early onset cancers and/or other objective "red flags" suggesting reasons to investigate for genetic problems in a person or family

- **Differential Etiology**: The presence or absence of genetic testing, and the scope of the testing, increasingly will be a part of differential etiology issues of great significance

- [Cite]

ToxicoGenomica

Case Specific Results in Benzene (Blood Cancer) and Mesothelioma Cases

Howard E. Jarvis, Esq.
Maron Marvel Bradley Anderson & Tardy LLC
Wilmington, DE

Study the Person to Determine Causation

- Risk factors for specific disease:
  - Smoking
  - Obesity
  - Family history of cancer, including:
    - Breast
    - Pancreatic
    - NHL
    - Melanoma

Evidence Genomic Instability

Genomics Supports

- Toxicology
- Population Epidemiology
- Oncology / Hematology
- Molecular Epidemiology

Next Generation Sequencing

Next Generation Sequencing of GERM-LINE DNA can reveal gene variants of predisposition to a cancer and help rule out the alleged causative agent and susceptibility to that agent triggering the predisposition

Genomic Analysis in Tort Cases

Results from Use of Genomic Analysis in Tort Cases: Creating Change and Driving New Outcomes

CASE SPECIFIC RESULTS IN BENZENE (BLOOD CANCER) AND MESOTHELIOMA CASES

Germline Mutations in MDS/AML Predisposition Disorders

Larry J. Chilton
Chilton Yambert Porter LLP
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Welcome to GenoPalate

You're unique. Your food should be too.

Just like the pattern in our fingerprints, our nutritional needs are unique to each and every person. When it comes to how we fuel our bodies, we now know that general nutrition guidelines, the latest supplement trends and fad diets simply don't work.

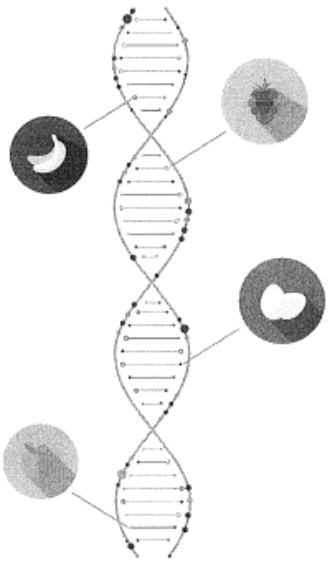
The key to feeling well and staying healthy is to know what to eat. This formula is contained in our DNA.

GenoPalate's Analysis unlocks this formula by analyzing over 100 different genetic variants related to nutrition.

Based on our findings, you'll find out...

- What macronutrient intake is ideal for you
- Your needs for 14 different vitamins and minerals
- How likely you are to be sensitive to lactose, gluten, caffeine and alcohol
- The 100+ best foods for you, based on your genes

Together we'll explore what it means to get your body the nutrients it really needs. We'll help you make specific, nourishing choices; crush your healthy lifestyle goals; and steer yourself down the right path—without wasting precious time or resources trying to figure it all out on your own.



Purpose of review
Recognition of hereditary hematopoietic malignancies impacts patient management as well as health surveillance strategies for the patient and relatives who share the causative DNA variant. In this review, barriers to the diagnosis and management of patients are outlined.

Recent findings
Increasingly, individuals are being recognized as having germline predisposition to hematopoietic malignancies. Clinical testing for these syndromes is difficult for most clinicians given the need to send true germline samples and the lack of standardization in the field with regard to which genes are covered and the types of DNA changes detected. Additional barriers such as insurance coverage, especially for older individuals, and access to clinical experts need to be overcome in the future.

Summary
New research addressing whether use of hematopoietic stem cells with deleterious variants are permissive to transplantation; effective means of delivering genetic counseling and results disclosure to decrease the psychological impact of these diagnoses; and a comprehensive list of all predisposition genes will advance our ability to provide the best treatment possible for our patients and facilitate strategies to maintain excellent health throughout their lifetimes and for members of younger generations.

Video abstract
Submitted, http://links.lww.com/COH/A22

Keywords
germline predisposition syndromes, hereditary hematopoietic malignancies, molecular profiling

Germline mutations in MDS/AML predisposition disorders

Lucy A. Godley, Curr Opin Hematol 2021, 28:86-93

INTRODUCTION

Inherited predisposition to hematopoietic malignancies is more common than previously appreciated [1–4]. As next-generation sequencing has been applied to families with clustering of hematopoietic and young-onset solid tumors, the list of predisposition genes that increase risk of hematopoietic tumors continues to expand (Tables 1–4). With greater numbers of genes and mutation types identified, the complexity of clinical testing also increases, challenging busy practitioners to diagnose patients accurately. Recognition of germline cancer predisposition also complicates planning for allogeneic stem cell transplantation in which relatives are often the preferred donors. In this review, challenges to diagnosis and patient management as well as ethical considerations will be presented.

CHALLENGES TO DIAGNOSIS

The idea that these syndromes are rare

Initial descriptions of hereditary hematopoietic malignancies (HHMs) asserted that they are rare, giving clinicians the impression that they would likely never encounter such patients in their practice. In addition, training programs for physicians,

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Germline mutations in MDS/AML predisposition disorders

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KEY POINTS

- Hereditary hematopoietic malignancies are being recognized increasingly, but challenges exist in diagnosing and managing patients effectively.
- Allogeneic stem cell transplantation preferentially uses related donors, and consideration of HHMs should be incorporated into standard operating procedures of all transplant programs, and more data are needed on when use of donor cells with deleterious germline variants are permissive to successful outcomes.
- Establishment of national centers of excellence, fostered by increasing patient advocacy and development of ethical standard practices, will improve our understanding of the natural history of germline predisposition syndromes leading to hematopoietic malignancies and may lead to intervention strategies to delay or even prevent development of cancer or other complications.

nurses, and genetic counselors either neglected to include these syndromes all together or focused on them as relevant only for pediatric populations. Consequently, adult oncologists generally do not consider these conditions routinely. If diagnostic tests are not sent, the diagnoses are never made, fulfilling the expectation that these conditions are not seen in adults. Once these notions are firmly held, it takes a tremendous amount of evidence to change prevailing thought.

The idea that germline variants pertain to people presenting at young ages

Compounding the failure to diagnose HHMs in adult populations regularly is the idea that deleterious germline variants only cause disease at younger ages. Although, it is true that people who present with cancer much earlier than the average age are likely to have germline risk, it does not follow that people who present with cancer at the average age do not have such risk. This is an incorrect assumption about cancer development that needs to be clarified in our teaching of cancer biology, since it has hindered advancement in understanding the etiology of cancer in the elderly.

Germline mutations in MDS/AML predisposition disorders

Lucy A. Godley, Curr Opin Hematol 2021, 28:86-93

CONCLUSION

This is an exciting time for molecular diagnostics, given increasing expertise in genomic sequencing and techniques to identify complex copy number variants. As we identify more germline predisposition genes and individuals with deleterious variants in those genes, we need to develop comprehensive treatment plans that include accommodations for the impact of these mutations on the function of hematopoietic stem cells and other organ function. We also need to provide supportive genetic counseling and clinical expertise to allow our patients to live the healthiest lives possible.

Germline mutations in MDS/AML predisposition disorders

Lucy A. Godley, Curr Opin Hematol 2021, 28:86-93

The University of Chicago Genetic Services - Hereditary Myeloid Malignancy Panel

Specimen Types Accepted

- **Blood**
- **Saliva**
- **Buccal**
- **Cultured Cells**
- **Extracted DNA**

Additional Information

- Blood or saliva samples are not accepted for this panel for patients with a history of MDS/Leukemia. Please send cultured skin fibroblasts instead

Genes

ACD ADA2 ALAS2 ANKRD26 ATG2B ATM BLM BRCA1 BRCA2 BRIP1 CBL
CEBPA CHEK2 CSF3R CTC1 CXCR4 DDX41 DKC1 DNAJC21 EFL1 EFTUD1
ELANE ERCC4 ERCC6L2 ETV6 FANCA FANCB FANCC FANCD2 FANCE FANCF
FANCG FANCI FANCL FANCM G6PC3 GATA1 GATA2 GFI1 GSKIP HAX1 IKZF1
JAK2 KDM1A LIG4 MBD4 MECOM MLH1 MPL MSH2 MSH6 NAF1 NBN
NF1 NHP2 NOP10 NPM1 PALB2 PARN PAX5 PMS2 POT1 PTPN11 RAD51
RAD51C RBBP6 RBM8A RECQL4 RPL11 RPL15 RPL26 RPL35A RPL5 RPS10
RPS19 RPS24 RPS26 RPS7 RTEL1 RUNX1 SAMD9 SAMD9L SBDS SH2B3
SLX4 SRP54 SRP72 TERC TERT TET2 TINF2 TP53 UBE2T USB1 VPS45
WAS WRAP53 XRCC2

MD Anderson Cancer Center - Hereditary Leukemia Clinic

Doctors estimate that about 5-10% of leukemia cases are connected to an inherited genetic disorder passed down from parent to child.

Knowing that a disease has a genetic component can change how doctors treat the patient.

Patients with leukemia or other hematologic malignancies talk with their doctor about testing if:

- Diagnosed with MDS or AML before age 40
- Diagnosed with MDS or AML and have a personal/ family history of thrombocytopenia
- Diagnosed with MDS or AML and their bone marrow has specific genetic mutations. Doctors routinely test for these mutations during diagnosis.
- One or more close relatives have had leukemia

If a patient tests positive for a hereditary leukemia and hematologic malignancy syndrome, immediate blood relatives (parents, siblings, children) typically have a 50% chance of carrying the same genetic disorder.

MD Anderson Cancer Center
Hereditary Leukemia Syndromes: What patients and their families should know

Certain genetic changes, or mutations, can increase a person's chances of developing cancer. These hereditary cancer syndromes can be passed down from parent to child. Hereditary leukemia is one of the newest areas experts are studying.

Researchers have identified a dozen unique syndromes for hereditary leukemia, and that list is growing every year.

In 2008, one of the first genes linked to leukemia -- *RUNX1* -- was identified and became available for genetic testing.

We've found that these genes can cause different types of leukemia and related conditions, including AML, myelodysplastic syndrome (MDS), acute lymphoblastic leukemia (ALL) and chronic lymphoblastic leukemia (CLL).

MD Anderson Cancer Center

Hereditary Leukemia Syndromes: What patients and their families should know

Cancer patients are only tested when there's a reason to think the disease has been inherited or a patients' family members are likely to have the syndrome. Based on that, at least 5% of all leukemia may be hereditary.

We know that certain drugs are potentially more likely to work for people with certain syndromes.

When a patient tests positive for one of these syndromes, in most cases there's a 50% chance that their siblings and their children each have the same syndrome. One of their parents likely has it as well.