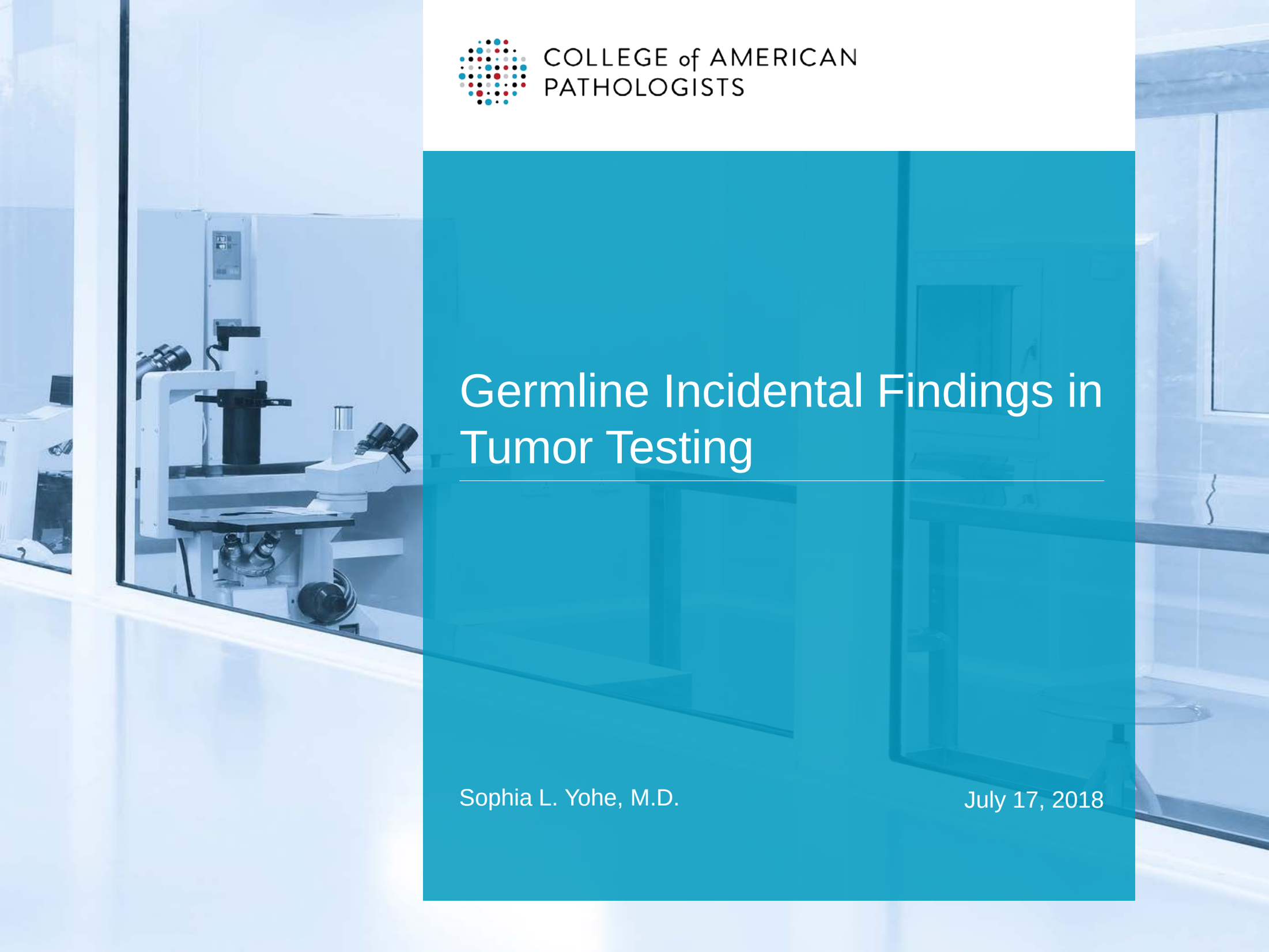

COLLEGE of AMERICAN PATHOLOGISTS

# Germline Incidental Findings in Tumor Testing

Sophia L. Yohe, M.D.

July 17, 2018

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# Sophia L. Yohe, MD

- **Associate professor at the University of Minnesota**
- **Program Director for the Molecular Genetic Pathology Fellowship**
- **Chair for the College of American Pathologist's Personalized Healthcare Committee (PHC).**

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- **I have no relevant financial disclosures**

# Workgroup

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- **Josh Lauring (ASCO)**
- **Marilyn Li (ACMGG)**

# Outline

- **Background information regarding incidental findings**
- **Which variants are incidental findings**
- **Existing recommendations regarding incidental findings**
- **Informed consent for incidental findings**
- **Barriers to reporting incidental findings in tumor testing**

# Definitions

| | |
|---|---|
| Incidental findings | Results that arise that are outside the original purpose for which the test or procedure was conducted |
| Anticipated | A finding that is known to be associated with a test or procedure |
| Unanticipated | A finding that could not have been anticipated given the current state of scientific knowledge |
| Secondary finding | A finding that is actively sought by a practitioner that is not the primary target |

# Background

- **Not new**
- **Physical exam**
  - **Finding a hyperpigmented skin lesion with irregular borders at a diabetes follow-up**
- **Radiology**
  - **“Incidentaloma”**
- **Occur at small rate in other laboratory areas**
- **More frequent with NGS/genomic methods**

# How common are incidental findings?

- **Depends on the definition**
  - **Any pathogenic/likely pathogenic in any gene**
  - **Pathogenic/likely pathogenic in only a subset of genes**
  - **Carrier status**
- **Depends of the breadth of testing and what findings are reported**
  - **Targeted panel**
  - **Large panel**
  - **Exome**
  - **Genome**
- **Depends on the tumor**

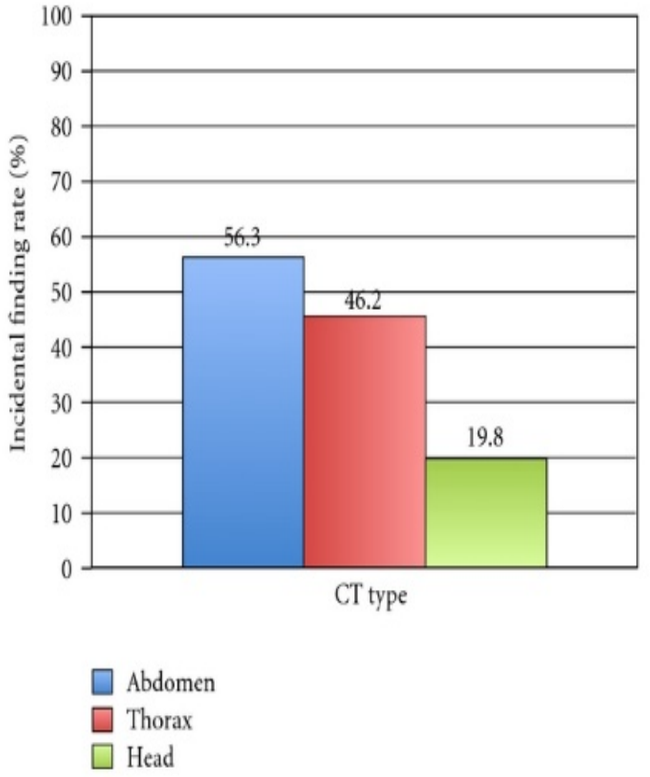
# Actual numbers

## Genomics

- **WES/WGS: 1-11%**
- **Cancer testing: 2.3-24%**

## Radiology

- **Trauma CTs: up to 33%**



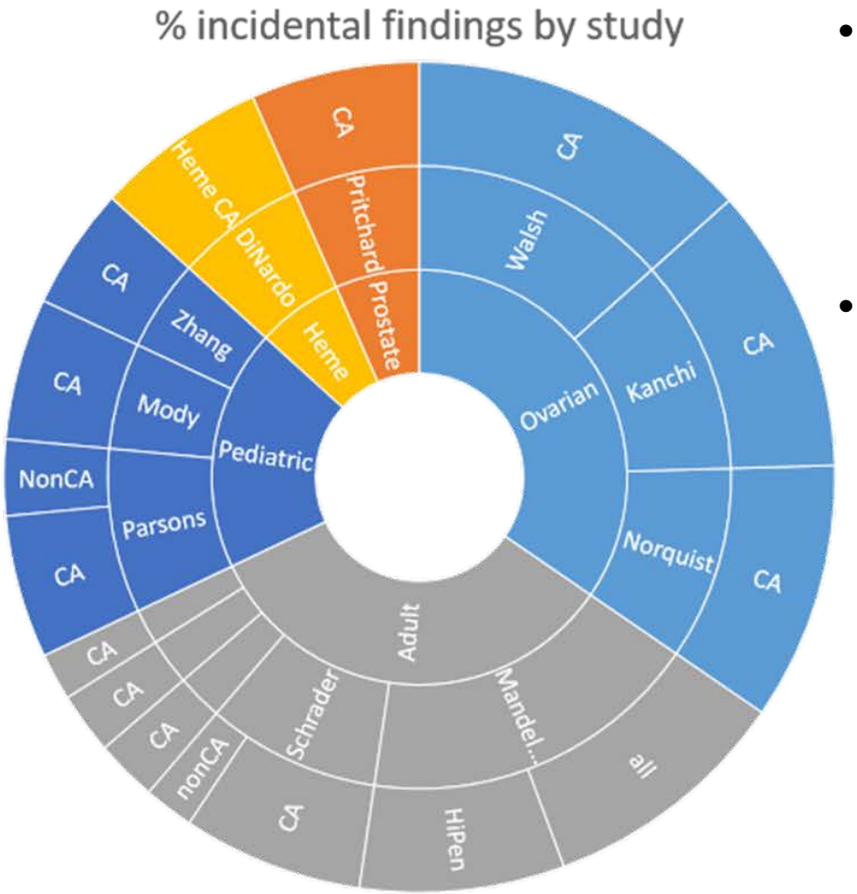

Thompson RJ, Wojcik SM, Grant WD, Ko PY. Incidental Findings on CT Scans in the Emergency Department. *Emerg Med Int*. 2011;2011:624847.

# Frequency of incidental findings in cancer

- Cancer predisposition more common than other incidental findings
  - Schrader, etal: 12.6% versus 3.5%
  - Parsons, etal: 10% versus 5.3%

- Frequency of cancer predisposition is dependent on tumor type
  - Ovarian cancer 18-24%
  - Prostate cancer 11.8%
  - Hematologic  12%

(these also used different genes)




- Definition of pathogenic variant
  - Jones: 3.3% truncating only

- Reported genes matter, Schrader
  - Cancer susceptibility 12.6%
  - Non CA susceptibility 3.5%
  - ACMGG list 6.4%

# Existing recommendations on whether to report incidental findings

- **ACMGG**
  - **All genome/exome (including tumor-normal)**
  - **Specific list of genes**
- **European Society of Human Genetics**
  - **Decision made at the local or national level with an ethical committee**
- **Danish Council of Ethics**
  - **Informed consent**
- **PHG Foundation**
  - **Clinically directed interpretation**
  - **Does not recommend looking for incidental or secondary findings**

# ACMGG Recommendations

- **2013**
  - **Minimum list constitutional mutations should be reported, regardless of the indication for test**
  - **56 genes**
  - **No opt out option for adults or children**
  - **Any constitutional tissue genome/exome**
- **2014**
  - **Clarification**
- **2016**
  - **Updated list of 52 genes**

# What constitutes an incidental finding in an NGS study?

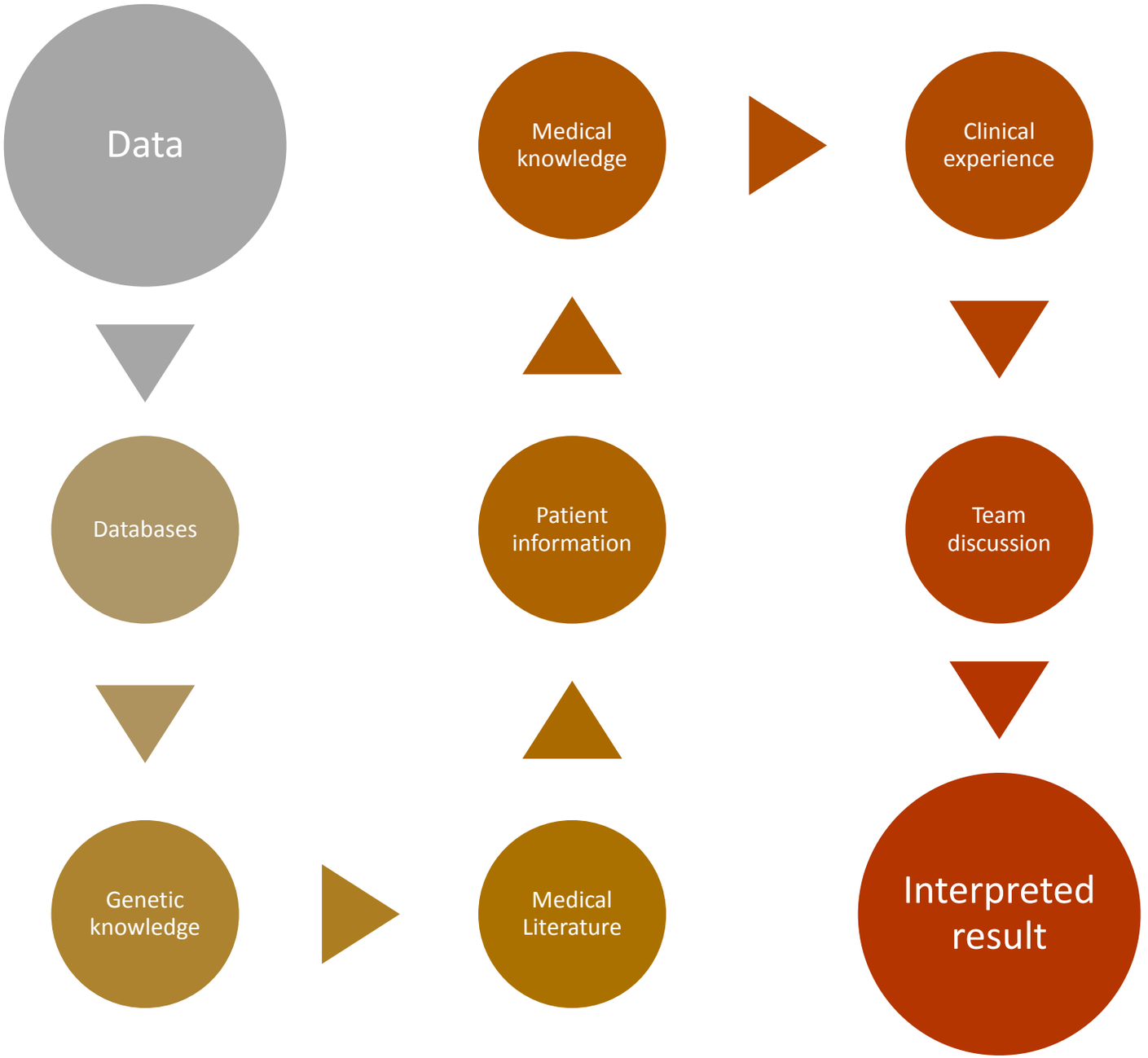
# What is a variant?

- **Any difference from the reference genome**
  - **3 to 4 million SNPs per genome (~20,000 per exome)**
  - **400,000 to 500,000 insertions and deletions (indels) per genome**
  - **In 2010, ~ 20% of SNPs and ~33% indels were be novel**
  - **Difference may not be “abnormal” or disease causing**
- **Reference genome**
  - **Genomic sequence from a single individual**
  - **Not a consensus**
  - **Does not represent “normal” or “benign” at each genomic position**

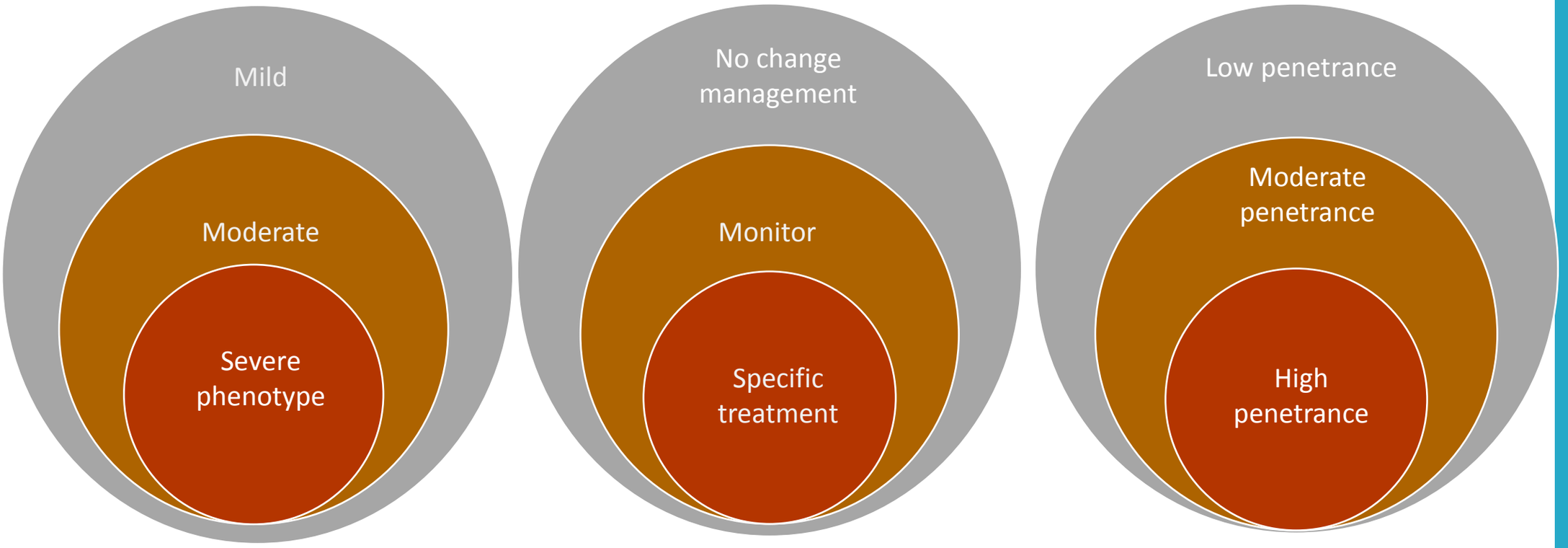
Whole-Genome Sequencing in Healthy People. Mayo Clinic Proceedings. 2017;92:159-172.

# Do we know enough about the variant?

- **Does the gene cause germline disease?**
- **Does it cause disease in this patient population?**
- **Is the variant pathogenic/likely pathogenic for germline disease?**



# What is significant?



# What is significant

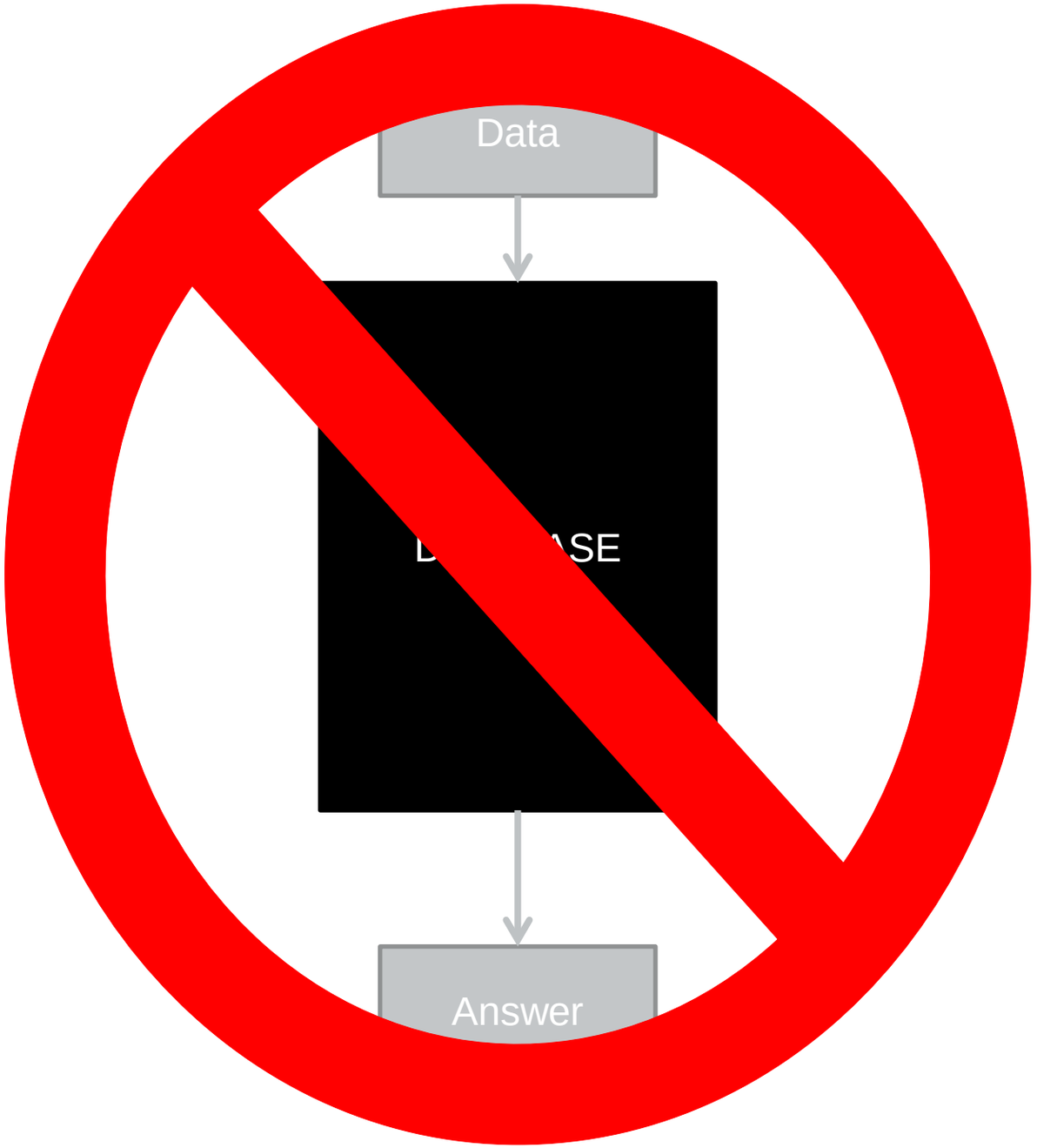
- **Should variants of undetermined significance be reported as an incidental or secondary finding?**
- **ACMGG recommends only reporting secondary findings with pathogenic or likely pathogenic variants**
- **There is controversy about which genes/disease warrant reporting as an incidental finding**
  - **There are suggestions from the ACMGG regarding this, however…**

# Pre test probability and penetrance

- **Positive predictive value depends on pre-test probability**
- **Penetrance estimates are based on years of testing symptomatic patients (higher pre-test probability)**
- **Actual penetrance may be lower if testing asymptomatic patients (lower pre-test probability)**
  - **Cancer susceptibility incidental findings**
  - **Other Mendelian disorders**

# Current use of databases

- **Population datasets**
  - **Frequency of a variant in a given population**
  - **Common variation**
- **Genotype/phenotype datasets**
  - **Is mutation associated with phenotype?**
- **Medical evidence**
  - **Databases**
  - **Literature**
  - **Clinical experience**



# Databases are incomplete, biased, and sometimes wrong

- **Novel variants**
- **Lack diversity**
  - **May lead to under or over interpretation of the significance of a variant**
- **Historic criteria for pathogenic were less stringent**

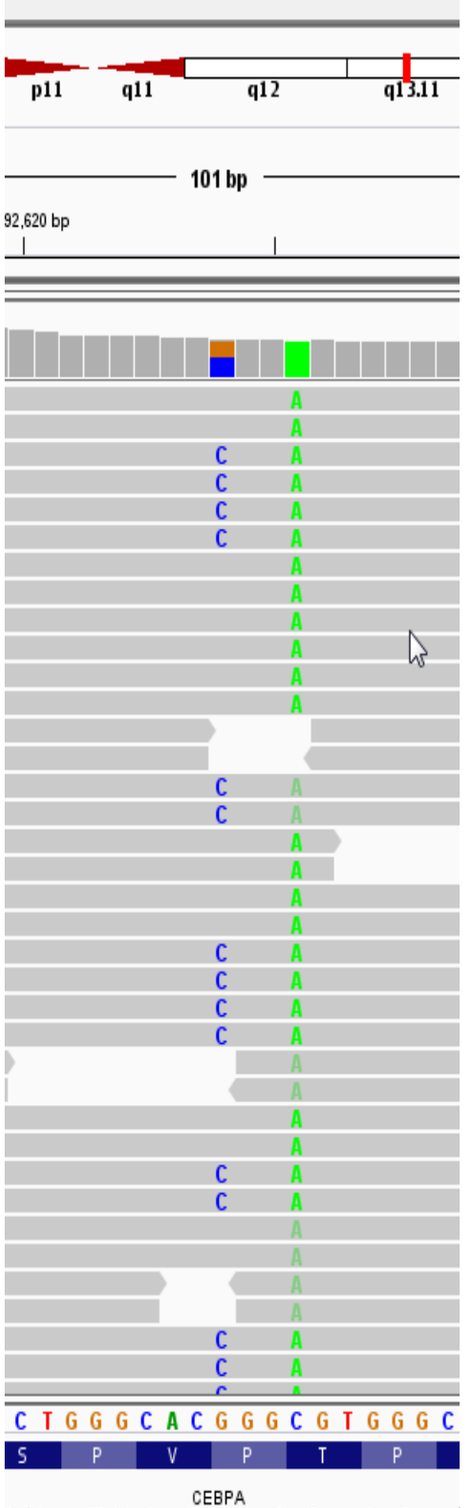
Manrai, et al. Genetic Misdiagnoses and the Potential for Health Disparities. *N Engl J Med.* 2016;375(7):655-665.
Carss, et al. Comprehensive Rare Variant Analysis via Whole-Genome Sequencing to Determine the Molecular Pathology of Inherited Retinal Disease. *Am J Hum Genet.* 2017;100(1):75-90.

# Practical impact

- **Since the original online posting of the ACMGG gene panel, it has changed twice including the *removal* of some genes**
- **With advancements in genomics, it is likely to change again including the addition and removal of genes**
- **For the unfortunate patients diagnosed with a disease because of an incidental finding within a gene *temporarily* on the ACMGG panel, the literal and figurative costs may be unacceptable**

# Is the variant germline or somatic?

- **Although VAF 50% or 100% suggest germline**
  - **Somatic mutations may have this VAF**
  - **Germline VAFs may vary significantly from 50% or 100%**
    - **Due to tumor aneuploidy**
    - **Variability and reproducibility of testing**
    - **Biased representation of one allele**
- **Unless germline is tested, cannot be definitive**






Thorvaldsdottir H, Robinson JT, Mesirov JP. Integrative Genomics Viewer (IGV): high-performance genomics data visualization and exploration. *Briefings in bioinformatics*. 2013;14(2):178-192.
Robinson JT, Thorvaldsdottir H, Winckler W et al. Integrative genomics viewer. *Nat Biotechnol*. 2011;29(1):24-26.

# Informed Consent for Incidental Findings

- **Standards for informed consent might differ between tumor and germline sequencing**
- **Not routine for somatic testing**
- **Review of history of informed consent in large-scale sequencing**
- **Discussion of systematic review by Ayuso et al in 2013, "Informed consent for whole-genome sequencing studies in the clinical setting - proposed recommendations on essential content and process."**
- **Stakeholders view by Mackley 2017**
- **Lack of specific literature addressing tumor genome sequencing**

# History

- **Human Genome Project completed 2003**
- **2009 NGS early clinical practice, often associated with research**
- **2012 TAT <2 months, cost <$10,000**
- **During this decade, informed consent and incidental findings ("return of results") were a hot topic but most publications regarded the research setting**
- **2013 more common in clinical practice**
- **Informed consent is not required for somatic testing**
  - **Not a new paradigm, eg Lynch syndrome and IHC**

# Research versus clinical

Rules relating to incidental findings in the research setting may not translate into clinical practice

**Research**

- **May be ethical to restrict research participation to subjects willing to receive incidental findings**
- **Testing often provided at no cost**

**Clinical**

- **Is NOT ethical to restrict clinical testing to patients who agree to accept incidental findings**
- **Typically paid for by third-party payers who may restrict testing to actionable targets**

# Informed consent for incidental findings germline sequencing

- **2013 Ayuso review of guidelines, professional recommendations about informed consent for WGS**
  - **Similar to the Basic HHS Policy for Protection of Human Research Subjects**
  - **Also stated consent should address the management of incidental findings and the study participant's to choose not to receive those findings**
  - **None of the sources addressed tumor genomics**
- **2017 Mackley reviewed stakeholder preferences**
  - **Great majority believed that incidental findings should be returned**
  - **Content of the disclosure determined by decisions made during consent**
  - **Autonomy**
  - **Stakeholders: patients, relatives, physicians, geneticists, researchers, IRBs, public**

# Cancer specific informed consent study

- **Forty patients with advanced cancer who had tumor genome profiling**
- **Decisional autonomy**
  - **Oncologists considered an invaluable resource for helping patients work through the decision process**
- **Patient wants:**
  - **To know if information would be beneficial to themselves or family members**
  - **To know whether such knowledge might have negative consequences**
  - **Sufficient time to weigh the decision (reflect, consult with others, and research)**
  - **Need to be factored into the logistics of meaningful informed consent**

Hamilton, et al. Decision-Making Preferences About Secondary Germline Findings That Arise From Tumor Genomic Profiling Among Patients With Advanced Cancers. *JCO Precision Oncology.* 2017.

# Informed Consent for Incidental Findings

- **Pre test and post test counseling**
- **Difference between cancer predisposition and other predisposition or disease genes**
  - **Cancer predisposition may be relevant to the cancer itself**
  - **Does it add value to analyze genes involved with other disorders such as cardiomyopathies**
  - **Balance the reality of how much information can be delivered to cancer patients and their families when their primary focus is on treatment of the cancer**
    - **People retain only a fraction of the information they receive**
    - **Information may be misremembered or misunderstood**
    - **Is consent truly informed regarding incidental findings when there is information overload related to a cancer diagnosis**

Weeks, et al. Patients' expectations about effects of chemotherapy for advanced cancer. *N Engl J Med.* 2012;367(17):1616-1625.

# Categories of germline incidental findings

*Anticipated incidental findings*

*Unanticipated incidental findings*

*Secondary findings in tumor-normal pairs*

# Anticipated incidental findings

- **Falls into ordinary lab practice and requires a policy to be implemented and followed.**
- **Without testing paired germline DNA, the laboratory should not be definitive about the source of the mutation (tumor or germline)**
  - **Raise the possibility of germline**
  - **Disclaimer that germline source cannot be excluded for any mutation**
  - **Using VAF of 50/100% is not foolproof for identifying germline**
  - **Wording of the report is important**
  - **Direct communication may be important**
- **PARP inhibitor and *BRCA1* mutation**

# Unanticipated incidental findings

- **Larger NGS panels are often sequenced and then bioinformatically masked to only show data from smaller panels**
- **Non-ordered genes may rarely be seen (QA, etc)**
  - **Minimize this**
  - **Address on a case by case basis**
- **A different question…should laboratories seek incidental findings if the gene is NOT ordered but is sequenced as part of the extensive panel and it is "recommended" (for example the ACMGG minimum list)**
- **Same issues about testing "tumor only" vs paired germline**

# Secondary findings in tumor-normal pairs

- **Paired tumor-normal samples for sequencing can reduce or eliminate germline variants from the reported tumor-specific variants**
- **Should laboratories actively seek incidental findings in the normal sample in specific genes and, if so, which genes and in which cases**
  - **If yes, have a protocol**
  - **“Rescuing” certain germline pathogenic variants from the filtering process.**
  - **Interpretation of normal tissue may require additional bioinformatics algorithms**
  - **May make sense for cancer predisposition genes (higher pre-test probability)**
  - **May not make sense for other genes**
- **More of an issue as panels get bigger -> exome -> genome**

# Barriers to reporting germline incidental findings during tumor testing

- **Patient related issues**
  - **Tumor sequencing is often performed in the setting of a new diagnosis of metastatic cancer where there is some urgency for the information provided by sequencing in order to choose the best therapy**
  - **Reflex testing may be in place to ensure timely and appropriate standard of care testing**
  - **Patients with advanced cancer may not expect to live to be impacted personally by germline variants and may prioritize information that will guide treatment**
  - **Incidental variants may have important ramifications in the patient with regard to medical management, or potentially, for the patient's family**

# Barriers to reporting germline incidental findings

- **Reflex testing**
  - **Standard operating procedures increase compliance with diagnostic testing guidelines and often result in quicker turn around times**
  - **Many are pathologist initiated when a histologic diagnosis is made**
  - **Germline genetic findings require patient consent, testing that anticipates such disclosure cannot be as easily streamlined into reflex testing**
    - **Abandoning reflex testing to allow for informed consent is not ideal**
    - **A tiered release of results is also not ideal**

# Barriers to reporting incidental germline findings in non-ordered genes during tumor testing

- **Compensation and Regulatory Considerations**
  - **A brief review of the historical coding and reimbursement for these procedures**
  - **Clinical validity and utility required for Medicare reimbursement**
  - **Coverage of gene panels varies**
  - **Seeking and reporting incidental findings in non-ordered genes may lead to problems with payment for the ordered test**

# Brief history of molecular reimbursement

- **“Stacking codes” each component of a molecular pathology procedure was coded separately**
- **Tier 1 & 2**
  - **Tier 1: gene specific information**
  - **Tier 2: arranged by the level of technical resources needed to perform a specific molecular analysis. Do not specify individual gene.**
- **Medicare reimbursement required**
  - **clinical validity: a result linked to a specific disease state**
  - **clinical utility: a result which is useful in medical decision making for the patient’s management**

# Variability in reimbursement approaches

- **Seeking and reporting incidental findings in non-ordered genes may lead to issues with payment for the test.**
  - **Some payers posit that if even a single reported gene lacks clinical utility, the entire gene panel lacks clinical utility and is not eligible for payment**
  - **In this scenario, reporting an incidental finding in a *non-ordered gene* may prevent payment for the *ordered test***
- **Other payers have taken the view that as long as a minimum specified member of genes in a panel have documented clinical utility, testing may be compensated even if other genes lack clinical utility**
- **Practices are not standard and a laboratory may have payers that use different structures.**

# Summary

- **The frequency of germline incidental findings during tumor testing depends on the number of genes analyzed and the definition of an incidental finding**
- **Clinical oncology panels have become larger and it is anticipated that this trend will continue with the possibility that tumor exomes may routinely be tested in the future**
- **With this trend, the detection of germline or potential incidental findings will increase**

# Summary

- **Different types of incidental findings may be found during cancer testing**
- **Recommendations regarding incidental findings are somewhat controversial, have changed over time, and were not designed for the setting of routine tumor testing**
- **There are several issues that impact the decision to seek and report incidental findings in tumor testing**
- **Guidance regarding incidental findings in cancer testing should consider the unique challenges in this setting**

# References


- Drazer et al. Prognostic tumor sequencing panels frequently identify germ line variants associated with hereditary hematopoietic malignancies. Blood Adv. 2018 Jan 23;2(2):146-150. PMID: 29365323. – 24%
- DiNardo et al., 2016. Evaluation of Patients and Families With Concern for Predispositions to Hematologic Malignancies Within the Hereditary Hematologic Malignancy Clinic (HHMC). Clin Lymphoma Myeloma Leuk. 2016 Jul;16(7):417-428. PMID: 27210295 – 18%
- Walsh et al., 2011. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proc Natl Acad Sci U S A. 2011 Nov 1;108(44):18032-7. PMID: 22006311 - 24%
- Kanchi et al., 2014. Integrated analysis of germline and somatic variants in ovarian cancer. Nat Commun. 2014;5:3156. PMID: 24448499 – 20%
- Norquist et al., 2016. Inherited Mutations in Women With Ovarian Carcinoma. JAMA Oncol. 2016 Apr;2(4):482-90. PMID: 26720728 – 18%
- Mandelker et al., 2017. Mutation Detection in Patients With Advanced Cancer by Universal Sequencing of Cancer-Related Genes in Tumor and Normal DNA vs Guideline-Based Germline Testing. JAMA. 2017 Sep 5;318(9):825-835. PMID: 28873162. – 17.5% - 76 genes
- Schrader et al., 2016. Germline Variants in Targeted Tumor Sequencing Using Matched Normal DNA. JAMA Oncol. 2016 Jan;2(1):104-11. PMID: 26556299. – 15.7% - - 187 germline genes
- Pritchard et al., 2016. Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer. N Engl J Med. 2016 Aug 4;375(5):443-53. PMID: 27433846. – 11.8%
- Zhang et al., 2015. Germline Mutations in Predisposition Genes in Pediatric Cancer. N Engl J Med. 2015 Dec 10;373(24):2336-2346. PMID: 26580448 – 8.5% - all cancers WES/WGS
- Seifert et al., 2016. Germline Analysis from Tumor-Germline Sequencing Dyads to Identify Clinically Actionable Secondary Findings. Clin Cancer Res. 2016 Aug 15;22(16):4087-4094. PMID: 27083775 – 4.3% - 36 hereditary cancer genes, highest in breast, CRC, ovarian, pancreas

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|---|---|---|
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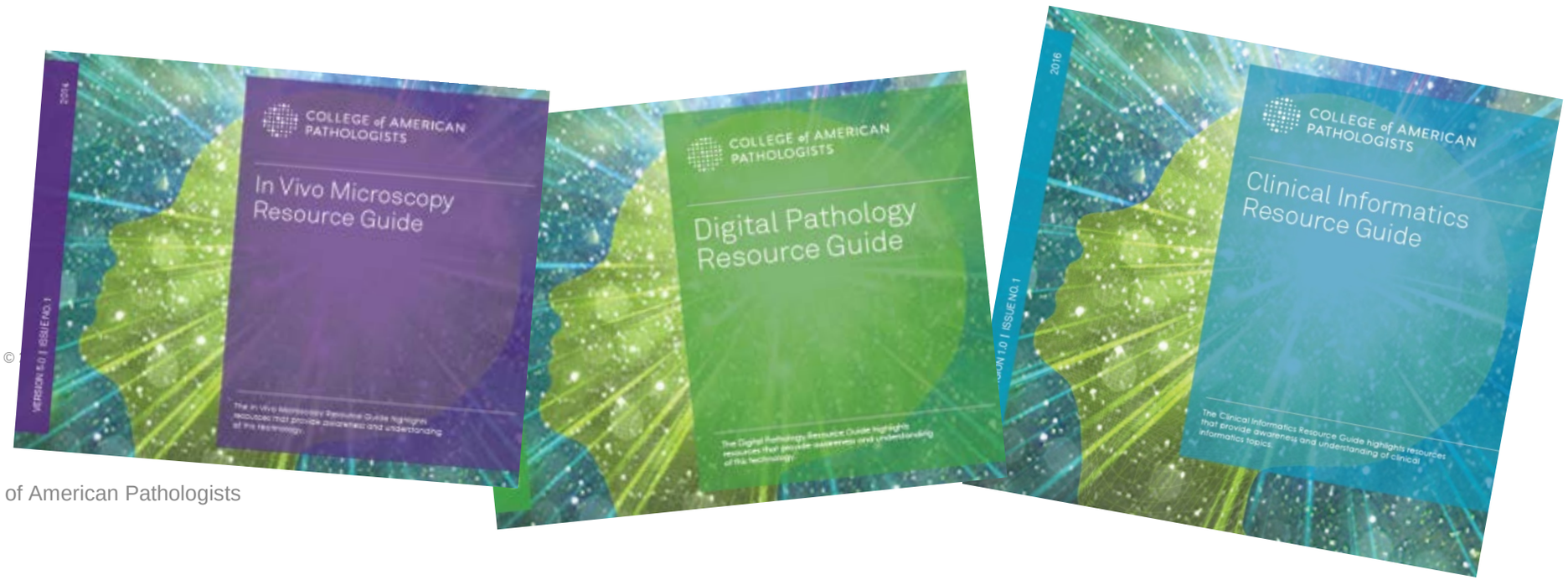

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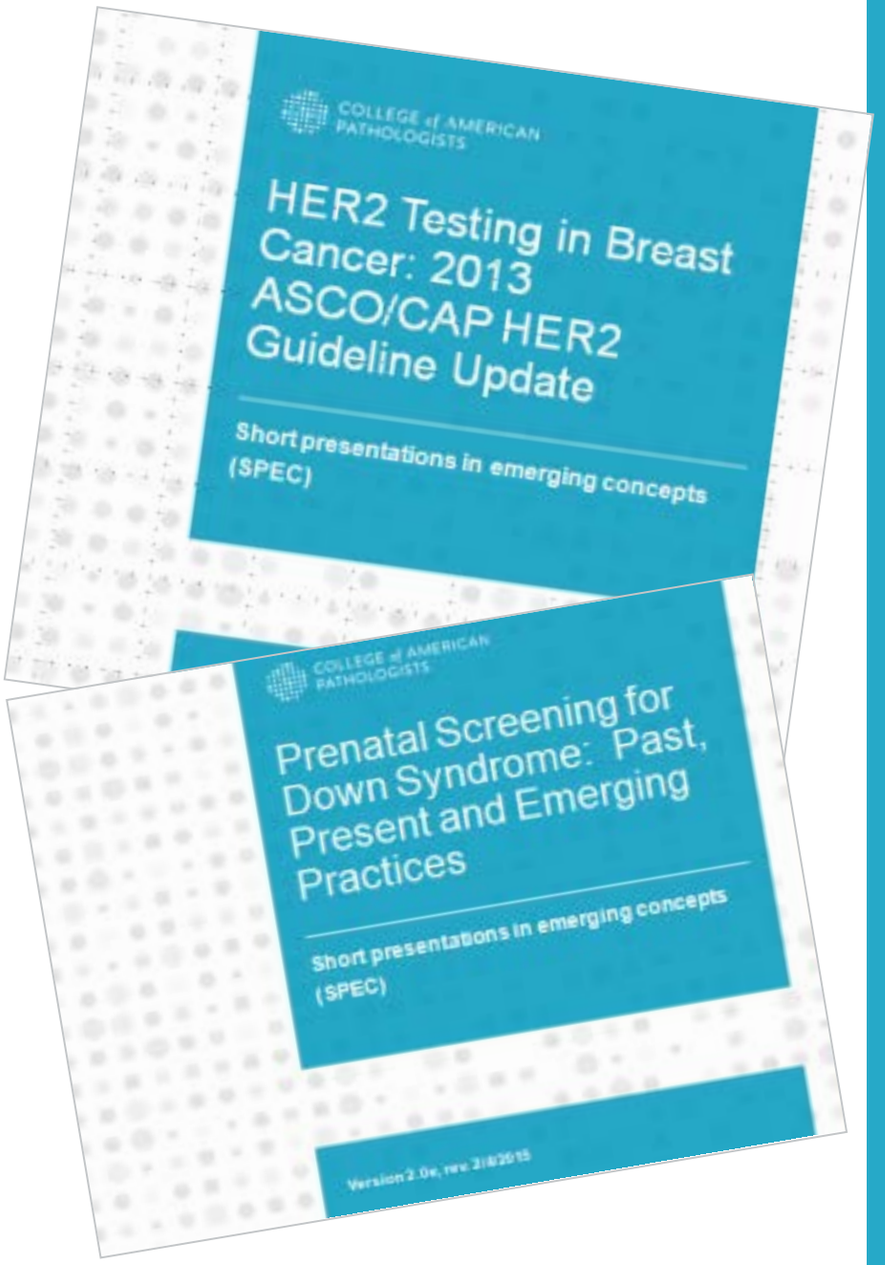

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