The ACMG Secondary Findings list: Intended Use and Applications to Research

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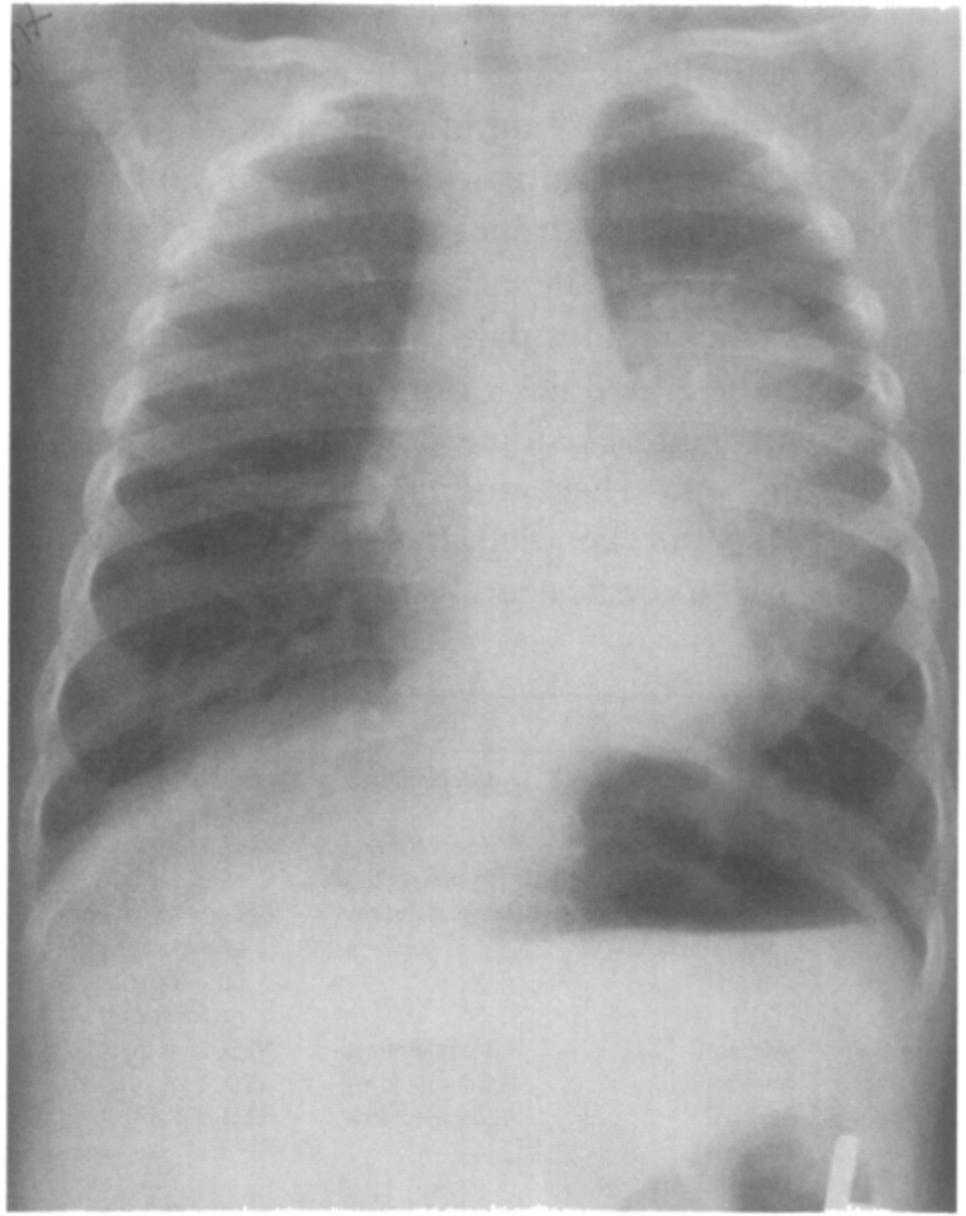
ACMG
American College of Medical Genetics and Genomics
Translating Genes Into Health®

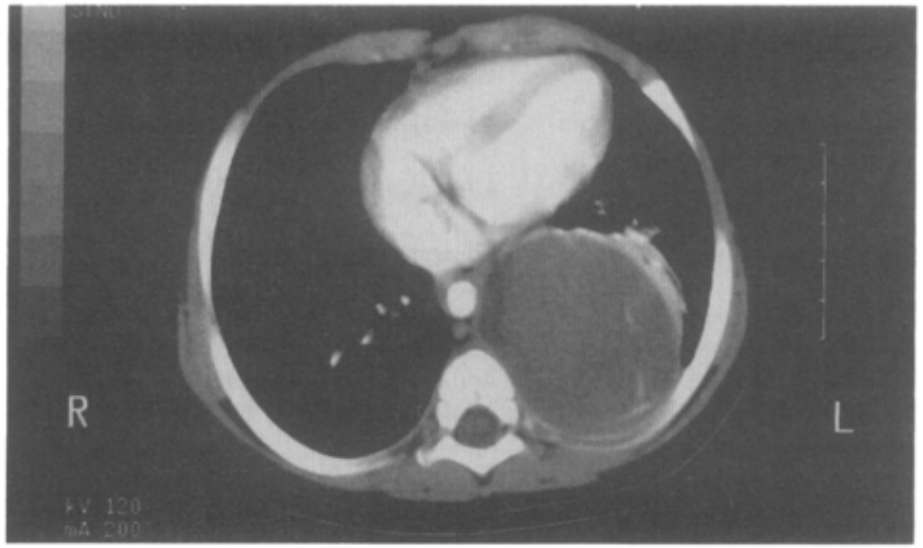
Financial Disclosure

Employee of Geisinger
Nothing to disclose—specifically no funding from Regeneron Pharmaceuticals

Case Study

- 15 mo old girl
- Daughter of missionaries working in TB endemic area
- Had received BCG vaccine
- Normal history and physical examination
- CXR recommended

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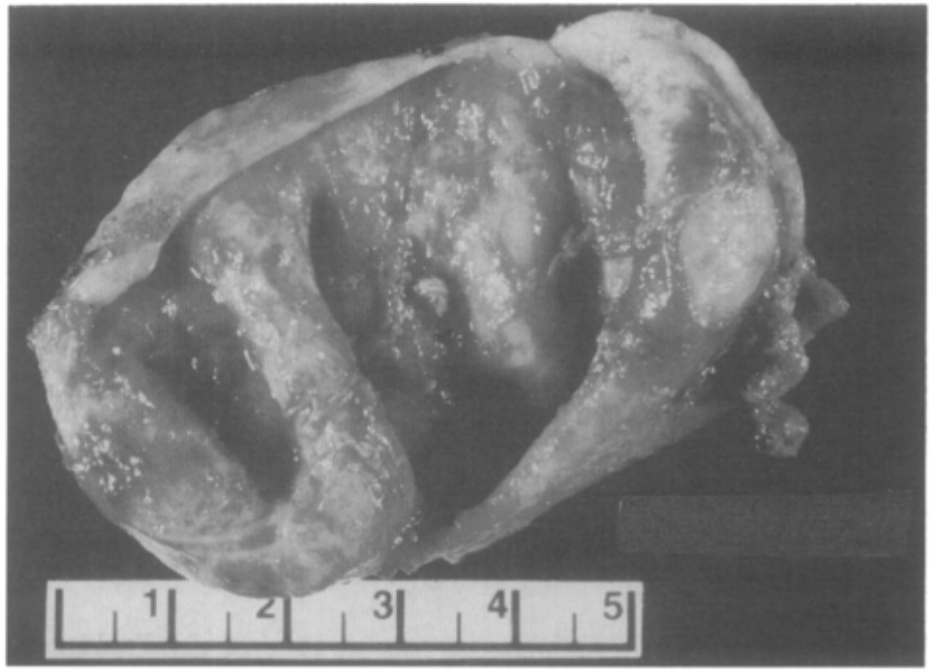
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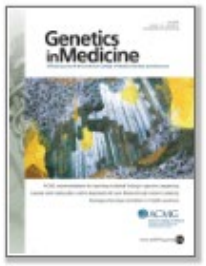
Incidental Findings

- Observations, results, or other findings that may occur during analysis but are unrelated to the goals of the analysis (Passalacqua NV, et al., In book: Ethics and Professionalism in Forensic Anthropology (pp.67-83))
- Most studied in radiology but can occur with any clinical intervention
- The clinical standard of care is that these are reported if deemed medically significant

Incidental Findings and Clinical Sequencing

- Sequencing is done for an indication (intellectual disability, multiple congenital anomalies)
- Information about variants in all genes is available with exome or genome sequencing
- Should analysis of sequence include genes that are medically important but not related to the indication (cancer predisposition, sudden cardiac death)?

Genetics in Medicine
Volume 15, Issue 7, July 2013, Pages 565-574



ACMG Policy Statement

ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing

Robert C. Green MD, MPH [1, 2] ✉, Jonathan S. Berg MD, PhD [3], Wayne W. Grody MD, PhD [4, 5, 6], Sarah S. Kalia ScM, CGC [1], Bruce R. Korf MD, PhD [7], Christa L. Martin PhD, FACMG [8], Amy L. McGuire JD, PhD [9], Robert L. Nussbaum MD [10], Julianne M. O'Daniel MS, CGC [3], Kelly E. Ormond MS, CGC [11], Heidi L. Rehm PhD, FACMG [2, 12], Michael S. Watson PhD, FACMG [13], Marc S. Williams MD, FACMG [14], Leslie G. Biesecker MD [15] ✉

2013 Statement (Version 1)

- Prior policy statement discussed alerting the patient to the possibility of such results in pretest patient discussions
- Convened Working Group
  - Year long consensus process
  - Open forum 2012 ACMG meeting
  - Review by outside experts
  - Created a minimum list (initially 56)

2013 Statement Recommendations

- Constitutional mutations found in the genes on the minimum list should be reported by the laboratory to the ordering clinician
  - Should be reported irrespective of the age of the patient
  - Constitutional analysis not tumor (somatic analysis)
- Only variants deemed pathogenic/likely pathogenic in these genes should be reported
- Ordering clinician provide pre- and post-test counseling
- Recommended against an ‘opt-out’ option

2013 Statement Caveats

- Insufficient data on penetrance and clinical utility to fully support these recommendations
- Needs to reflect current technology for variant detection and interpretation
- Did not address sequencing used for population screening
- Research: “Although we hope that investigators find our process and these recommendations useful in their attempts to design thresholds and lists for the return of genomic findings to research participants, we did not design this list for that purpose.”

Genetics in Medicine
Volume 19, Issue 2, February 2017, Pages 249-255

ACMG Statement

Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics

Sarah S. Kalia ScM [1], Kathy Adelman [2], Sherri J. Bale PhD [3], Wendy K. Chung MD, PhD [4, 5], Christine Eng MD [6], James P. Evans MD, PhD [7], Gail E. Herman MD, PhD [8], Sophia B. Hufnagel MD [9], Teri E. Klein PhD [10], Bruce R. Korf MD, PhD [11], Kent D. McKelvey MD [12, 13], Kelly E. Ormond MS [10], C. Sue Richards PhD [14], Christopher N. Vlangos PhD [15], Michael Watson PhD [16], Christa L. Martin PhD [17] ✉, David T. Miller MD, PhD [18] ✉, ; on behalf of the ACMG Secondary Findings Maintenance Working Group

2017 Statement (Version 2)

- Revised the terminology to “secondary findings” because these genes are intentionally being analyzed, as opposed to genetic variants found incidentally or accidentally
- Option to opt-out of receiving SFs for individuals undergoing clinical genomic sequencing (based on ACMG member feedback)
- Introduced a nomination process for genes to be added or removed
- List 59 genes

2017 Statement Methodologic Changes/Caveats

- Introduced a nomination process for genes to be added or removed
- Emphasized need for evidence of clinical utility
- Introduced use of a semiquantitative metric for determining actionability that is consistent with the approach of the ClinGen Actionability Working Group
- Recognized still limited evidence regarding penetrance
- Does not speak to research results

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ACMG Statement

ACMG SF v3.0 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG)

David T. Miller [1], Kristy Lee [2], Wendy K. Chung [3], Adam S. Gordon [4], Gail E. Herman [5], Teri E. Klein [6], Douglas R. Stewart [7], Laura M. Amendola [8], Kathy Adelman [9], Sherri J. Bale [10], Michael H. Gollob [11], Steven M. Harrison [12], Ray E. Hershberger [13], Kent McKelvey [14], C. Sue Richards [15], Christopher N. Vlangos [16], Michael S. Watson [17], Christa Lese Martin [18], ACMG Secondary Findings Working Group [19]

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Volume 23, Issue 8, August 2021, Pages 1391-1398

ACMG Statement

Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2021 update: a policy statement of the American College of Medical Genetics and Genomics (ACMG)

David T. Miller [1], Kristy Lee [2], Adam S. Gordon [3], Laura M. Amendola [4], Kathy Adelman [5], Sherri J. Bale [6], Wendy K. Chung [7], Michael H. Gollob [8], Steven M. Harrison [9], Gail E. Herman [10], Ray E. Hershberger [11], Teri E. Klein [12], Kent McKelvey [13], C. Sue Richards [14], Christopher N. Vlangos [15], Douglas R. Stewart [16], Michael S. Watson [17], Christa Lese Martin [18], ACMG Secondary Findings Working Group [19]

2021 Recommendations and Caveats

- Methodology much more explicit and transparent
  - Rationale for inclusion and exclusion of nominated genes provided
- Nomination process includes genes with ClinGen Actionability scores >10
- Emphasized the ACMG SF list was not validated for general population screening. Established two WGs
  - Genomic Screening of Asymptomatic Patients Working Group
  - Population Screening Working Group
- Focus is on clinical testing not research
  - “Researchers, in consultation with their local IRB, should decide on the appropriateness of return of SFs for their study”


WHY
Why couldn't i do it why ? Why couldn't i do it why ? Why couldn't i do it why ? Why couldn't i do it why ? Why couldn't i do it why ?
d - tears and a life in flames. difference choices. time can't be changed - tears and a life in flames. difference choices. time can't be changed - tears and a life in flames. difference choices
Why couldn't i do it why ? Why couldn't i do it why ? Why couldn't i do it why ? Why couldn...

Possible Reasons

- Most visible list of secondary finding genes
- Defined as a minimum list leaving discretion to add based on local context
- Has been used by high profile research projects focused on genomic return of results (eMERGE, MyCode)
- Uses explicit and transparent methodology
- Laboratories have developed analytic pipelines for analyzing SF genes
- Updated annually to reflect latest knowledge and technologies

Secondary Findings in Research

- “Researchers, in consultation with their local IRB, should decide on the appropriateness of return of SFs for their study”
- Which secondary findings to return, how they are returned, and whether updating is appropriate for longitudinal studies is at the discretion of the investigators and IRB
- If secondary findings are to be returned, this must be addressed in informed consent, including whether opt out is allowed
- Provisions for transition of care to clinical providers should be considered
- Resources needed for return must be accounted for
- Approach must comply with all relevant rules and regulations regarding health and genomic information

What do participants want?