Should we substantially limit the reporting of incidental findings?

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My initial hypotheses & biases

- I’m quite troubled by the potential difficulty in effectively classifying variants on the ACMG59 for reporting incidental findings (IF).
- Some have clear loss of function alleles and phenotypes but missense alleles are very difficult to classify.
- ACMG classification rules may improve our ability to do this but still not easy.
- Reclassification from pathogenic to benign is clinically troubling, particularly in the incidental setting (do no harm).
- Some genes maybe too new to know the spectrum well.
- Some genes have very broad phenotypes so what exactly is patient at risk for?
- My starting bias was reporting of IF in cancer genes is easier (but not simple) compared with cardiovascular genes.

Based on clinical reporting of pathogenic variant in (Alfares AA, et al. *GIM, 2015*)

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Genetic Misdiagnoses and the Potential for Health Disparities

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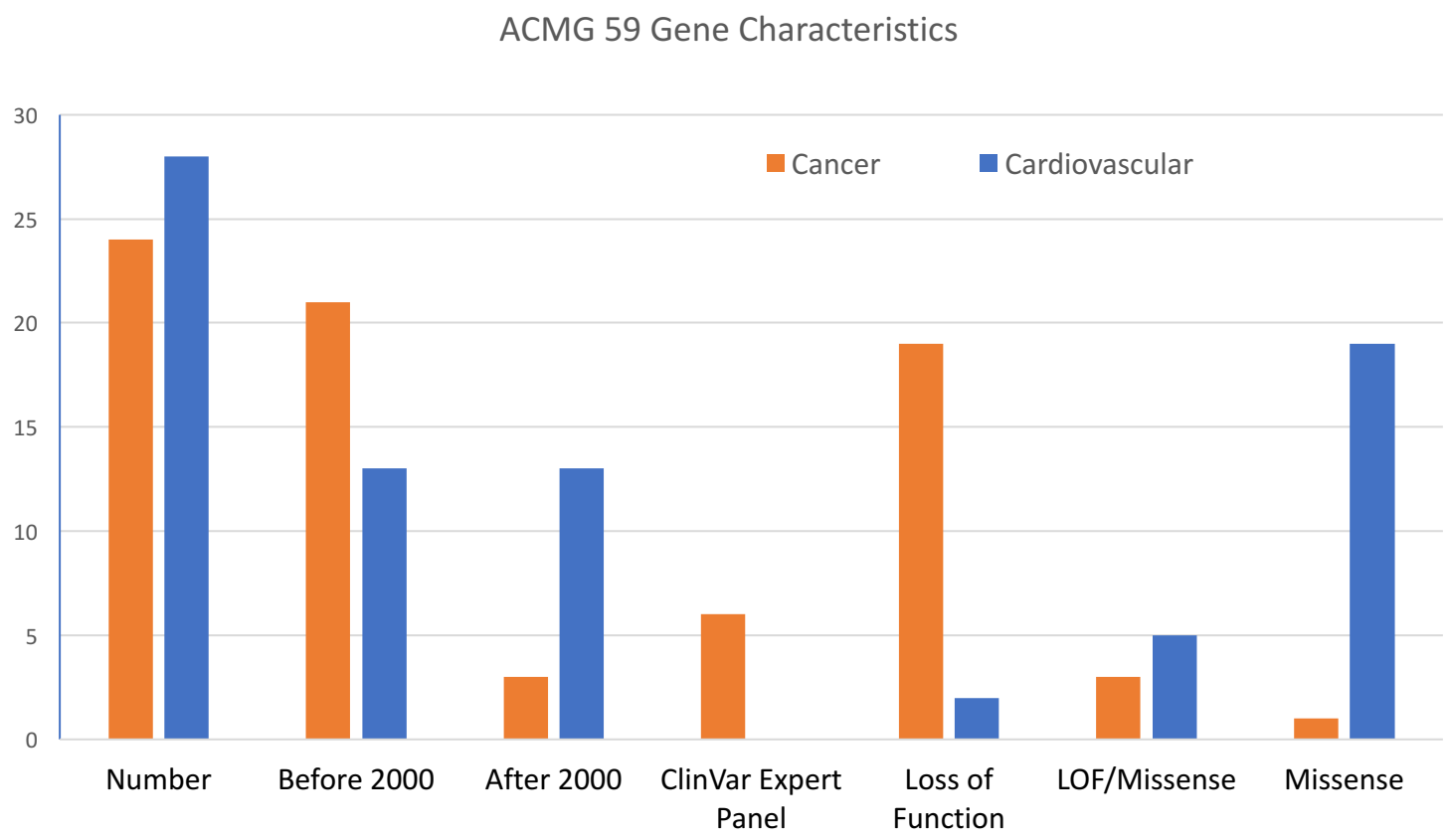
Examples of reclassification from Pathogenic to Benign (or LB)

1. 2004 - 29 yr old postdoc with retinal hemangioma. VHL done at ”top” lab – c.340+5G>C clearly stated to be pathogenic with mRNA defect described on the report.
   - 12 years later in for follow-up at another center. No other features of VHL developed (although only intermittent screening)
   - Now BENIGN in ClinVar – 4.5% frequency in Han Chinese (patient is Chinese).
2. *DSP* c.88G>A (p.V30M) IF in child in 2013
   - Now reclassified based on frequency in ExAC data as BENIGN
3. LDLR missense variant reported as pathogenic (c.58G>A (p.G20R) in both symptomatic patient and IF
   - Now classified as VUS based on ACMG rules although still very rare and not completely clear to me why it was reclassified?

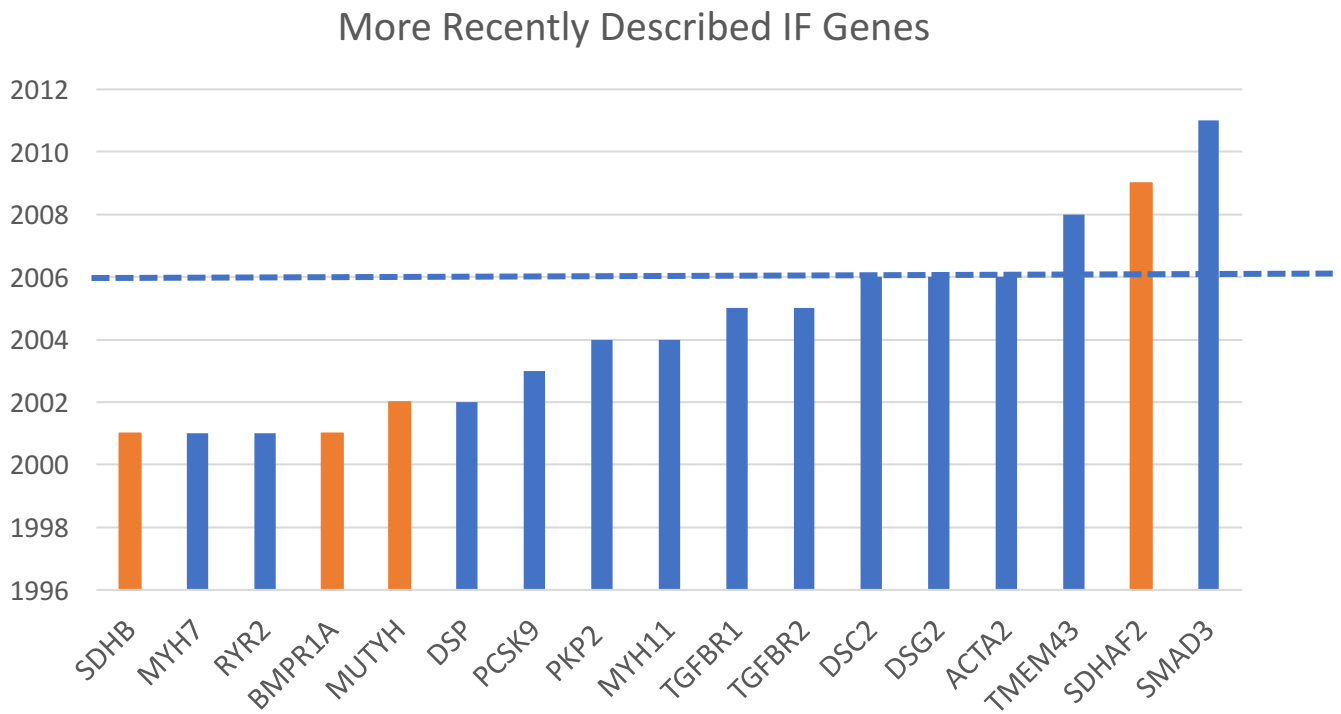
Method

- Took the ACMG59 list
  - Focused on cancer (n=24) and cardiovascular (n=28) genes
- Reviewed each one in OMIM and other references and assessed:
  - Date gene-variant/disease first published (before or after 2000)
  - Looked at majority of disease variants (truncating, mix of LOF/missense, or primarily missense)
  - Looked at other features – how many reported cases, variety of variants
  - Looked at Mendelian segregation and phenotypic heterogeneity
  - Presence of an Expert Panel in ClinVar

Overview of the ACMG59 Genes



However, even newer genes aren't that new



Other complications for interpretation/implementation as IF

- Although most conditions are autosomal dominant there are other Mendelian conditions:
  - X-linked – Fabry (do you report both males & females)?
  - Autosomal recessive – MUTYH (do you report single carriers)?
  - Many genes have both dominant and more severe recessive phenotypes – complicates counseling
  - Digenic conditions – again do you report a single allele?
- A few conditions have only a few known disease alleles/founders.
  - Perhaps only report these well documented ones, e.g. TMEM43, SDHAF2

Extraordinarily wide range of alleles and quality of information

- Some genes, e.g. BRCA1 have thousands of documented alleles (LOF and missense) with Expert Panel interpretation
- Some genes have a few well documented alleles and then a range of other rare ones (MUTYH)
- Some extremely rare conditions with little allele information (CACNA1S, ACTC1)
- A number of other “messy genetics”
  - PMS2 – numerous pseudogenes may report “wrong” allele
  - Genetic modifiers - do labs have to look for those if they substantially impact the at-risk phenotype

My conclusion

- I'm not clear we are doing overall good reporting IF's
- Reporting variants in many of these genes is difficult despite decades of knowledge!
- Should consider substantial simplification of the current IF recommendations if we continue reporting them
  - Consider dropping some of the very rare or recessive conditions unless quite common
  - Develop specific IF rules/technical guidance for each gene on the ACMG59
    - Strict LOF definition
    - From single to panel of missense to report (perhaps update yearly)
    - Any other gene specific complications (common modifier)
  - Develop a one sheet IF description including any lab guidance, clinical aspects, next steps for each gene on list:
    - Similar to the newborn screening fact sheets