REPORTING OF SECONDARY FINDINGS IN CLINICAL GENOMIC SEQUENCING: NATIONAL GUIDELINES ARE REQUIRED

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INTRODUCTION

- The rapid and growing integration of exome and genome sequencing into clinical genetic diagnosis raises awareness regarding the identification of **germline variants unrelated to the primary reason for testing but of relevance to the health and/or reproductive choices of the patient or the patient's family (secondary findings, SFs);** for the purpose of this presentation, we consider that SFs result from deliberate screenings.

- It is estimated that **1 in 38 (2,7%) healthy individuals of European descent has a (likely) pathogenic variant in a medically actionable dominant disease gene** (Haer-Wigman L *et al*., EJHG, 2019).

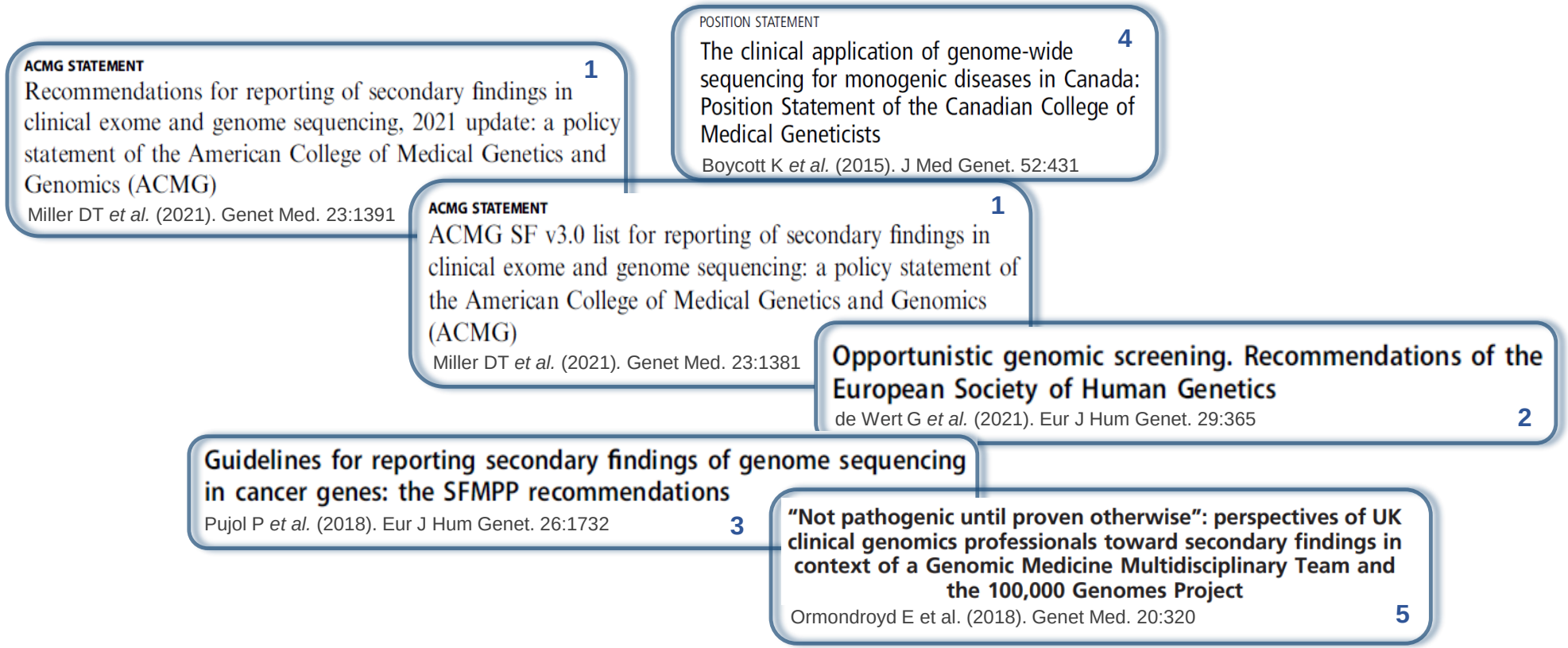
- The reporting of SFs offers an unique opportunity to identify and mitigate disease that may otherwise be unrecognized in an individual but also poses **major challenges**, as **multiple issues** (medical, ethical, legal, economic) and **different contexts** (e.g. paediatric and prenatal diagnosis, patient and family management, research in rare diseases) **must be considered**, highlighting the **importance to promote standardized reporting of SFs.**

- There is an ongoing debate among medical genetics societies worldwide, and the general public, on whether, how and when SFs are to be disclosed.

- We aim to bring to the consideration of the Portuguese Society of Human Genetics (SPGH) the **urgent need for issuing national guidelines for reporting SFs from clinical genomic sequencing.**

METHODOLOGY

- Consultation and review of guidelines for reporting SFs in clinical genomic sequencing from several medical genetics societies, focusing on the ones published by the American College of Medical Genetics and Genomics (ACMG), the European Society of Human Genetics (ESHG) and the French Society of Predictive and Personalized Medicine (SFMPP).



RESULTS

	RECOMMENDATIONS FOR REPORTING SECONDARY FINDINGS IN CLINICAL GENOMIC SEQUENCING				
	ACMG_2021[1]	**ESHG_2021[2]**	**SFMPP_2018[3]**	**CCMG_2015[4]**	**UK clinical genomics professionals_2018[5]**
Reporting SFs to the patient	YES (SF v3.0 – routine analysis of 73 clinically actionable genes mainly related to cancer and cardiovascular diseases, regardless of the age of the patient)	NO (*in silico* gene panels specific to the primary indication for testing should be used; however, if opportunistic genomic screening is offered, it should be embedded in adequate pilot and evaluation studies)	YES (SF v1.0 – routine analysis of 36 clinically actionable cancer genes in adults)	NO (*in silico* gene panels specific to the primary indication for testing should be used; however, it is recognized that some clinical laboratories may wish to report SF)	YES (but restricted to medically actionable, higher penetrance and serious conditions; a cautious approach that continually incorporates evidence is favored)
Spectrum of SFs to be reported	Pathogenic and likely pathogenic variants	Highly penetrant, medically actionable variants	Only pathogenic variants	Highly penetrant, medically actionable variants	Limited, highly likely pathogenic variants
Respect for patient's autonomy and right not to know	YES	YES (however, professional duty overrules patient's autonomy in the case of specific findings of great importance for the patient's own health)	YES	YES	YES
Disclosing risk for adult-onset conditions in minors	YES	NO	Not applicable	NO (exceptions)	Not applicable
Multi-step informed consent for SF	NO	May be helpful but needs further empirical study	YES	Not addressed	Not addresssed

Table 1. Comparison of several international guidelines for reporting secondary findings in clinical genomic sequencing.

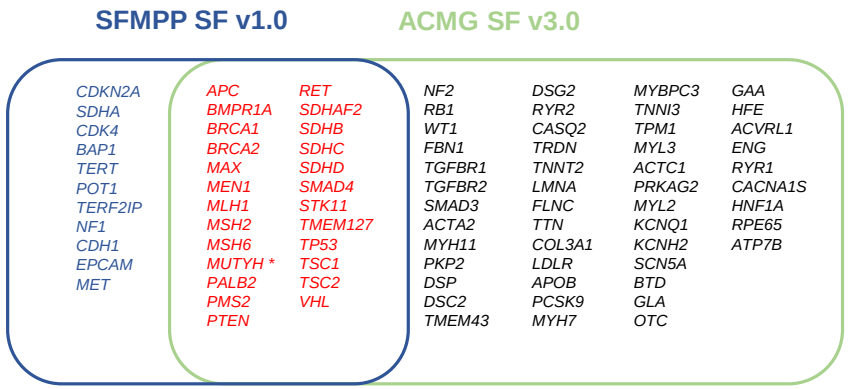


Figure 1. Lists of medically actionable genes proposed by the SFMPP (36 cancer genes) and the ACMG (v3.0, 73 genes related to cancer, cardiovascular, inborn errors of metabolism and miscellaneous phenotypes). Shown in red are the cancer genes that coincide in both lists; **MUTYH* causal variants are only reported when present in homozygosity/compound heterozygosity.

DISCUSSION

- Considering the diversity of approaches and the complexity involved in reporting SFs, we propose that **the SPGH should promote the creation of a multidisciplinary workgroup involving all the stakeholders (medical specialists, medical and clinical laboratory geneticists, ethicists, lawyers, patient's representatives, psychologists) to elaborate national guidelines to harmonize the report of SFs in clinical genomic sequencing.**

- **A few loose considerations regarding SFs to reflect upon:**

  - It is expected that SFs disclosure has the potential to prevent serious morbidity and mortality, however data on actual clinical utility, cost impact and cost-effectiveness of disclosing SFs are limited; aditionally, little is known about patient's response to SFs psychologically, medically, or regarding communication with relatives and further studies are neeeded.
  - Lists of conditions and associated genes have been criticized based on the fact that variants might be less pathogenic and less penetrant in the absence of a phenotype or family history of the associated disease; hence, the identification of SFs as predictive disease risks might be questionable and lead to excessive medicalization.
  - Both the ACMG and the SFMPP recommend to only return bi-allelic SFs in recessive diseases, but one may wonder whether it would not be relevant to also return carrier status (e.g. *CFTR,* for reproductive decisions).
  - There is a major need to improve the quality and standardize the information given to patients regarding the clinical utility of SFs.