



# Biobanks could identify medically actionable findings relevant for COVID-19 clinical care

**To the Editor** — DNA biobanks have the potential to provide real-time clinical utility during this COVID-19 pandemic by identifying patients with underlying genetic conditions that could result in a higher risk for COVID-19-related morbidity or mortality. Medically actionable genetic findings are generally considered to be genetic changes that reveal or predict a genetic condition for which preventive measures and/or treatments are available<sup>1,2</sup>. In 2013, the American College of Medical Genetics and Genomics (ACMG) recommended the reporting of medically actionable secondary findings identified during routine clinical exome and genome sequencing<sup>1</sup>, and in 2016 the ACMG updated this list to include 59 genes for genetic conditions they deemed to meet criteria for medical actionability (i.e., ACMG59)<sup>3</sup>. Although these ACMG recommendations were not intended to become a definitive statement on genetic conditions that are or are not medically actionable, the ACMG59 list has become a default standard across multiple DNA biobanks, in which sequencing has identified that roughly 3% of the population harbors a deleterious variant in one of these genes<sup>4</sup>. While the overall clinical impact of returning unanticipated genomic findings is still being studied, early findings in some categories indicate evidence of its potential impact on improving patient outcomes<sup>5</sup>.

More recently, ongoing efforts from the Clinical Genome Resource Actionability Working Group have highlighted over 150 medically actionable genetic conditions<sup>2</sup>. Using the ACMG59 and Clinical Genome Resource actionability curations as a reference, we have identified over 70 genetic conditions that could be relevant to making clinical decisions for patients who have developed COVID-19 (Table 1). These genetic conditions can broadly be split into three main categories: (1) conditions associated with an increased susceptibility to medications commonly used in managing COVID-19 and respiratory failure; (2) conditions that cause reversible metabolic or thrombotic crises that are often induced by severe illnesses such as COVID-19; and (3) conditions that cause reversible cardiopulmonary complications that can be exacerbated during severe illnesses such as COVID-19. Although knowledge of a patient's status for one of these conditions

**Table 1 | Potential COVID-19-related medically actionable genetic conditions**

Class of actionable condition	Genetic condition	Gene(s)
Conditions associated with an increased susceptibility to medications commonly used in managing COVID-19 and respiratory failure	Long QT syndromes and catecholaminergic polymorphic VT	CASQ2, KCNE1, KCNH2 <sup>a,b</sup> , KCNQ1 <sup>a,b</sup> , RYR2 <sup>a,b</sup> , SCN5A <sup>a,b</sup>
	G6PD deficiency	G6PD
	Malignant hyperthermia susceptibility	CACNA1S <sup>a,b</sup> , RYR1 <sup>a,b</sup>
Conditions that cause reversible metabolic or thrombotic crises that are often induced by severe illnesses	Urea cycle disorders	ASL, ASS1, CPS1, NAGS, OTC <sup>a,b</sup> , SLC25A13 <sup>b</sup> , SLC25A15
	Lysinuric protein intolerance	SLC7A7
	Fatty acid oxidation disorders	ACADM, ACADVL <sup>b</sup> , CPT2, ETFA, ETFB, ETFDH
	Acute porphyrias	CPOX, HMBS <sup>b</sup> , PPOX
	Adrenal insufficiency disorders	AAAS, ABCD1 <sup>b</sup> , AIRE, LHX4, PCSK1, PROP1
	Hereditary thrombophilia	PROC <sup>b</sup> , PROS1 <sup>b</sup> , SERPINC1
	Methylmalonic acidemia	MMACHC <sup>b</sup> , MMADHC <sup>b</sup>
	Atypical hemolytic uremic syndrome	C3, CD46, CFB, CFH, CFI
	Conditions that cause reversible cardiopulmonary complications that can be exacerbated during severe illnesses	Familial cardiomyopathies
Cystic fibrosis		CFTR
Refsum disease		PEX7, PHYH
Familial pulmonary hypertension		BMPR2 <sup>b</sup>
Congenital myasthenic syndrome		CHRNA1, CHRNB1, CHRND, CHRNE, COLQ, CHAT, GFPT1, MUSK, DOK7, RAPS N

<sup>a</sup>ACMG59 actionable gene. <sup>b</sup>Clinical Genome Resource actionable gene.

will not protect them from developing COVID-19, it may indicate potential complexity and allow clinicians to anticipate and mitigate morbidity or mortality associated with their clinical management.

Academic and national biobanks are well positioned to quickly initiate a clinical workflow for returning these medically actionable findings, as many have already accrued a critical mass of genotyping and sequencing data, and many of these biobanks already have in place the governance infrastructure for returning clinically actionable genetic findings to patients. □

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## References

- Green, R. C. et al. *Genet. Med.* **15**, 565–574 (2013).
- Webber, E. M. et al. *Hum. Mutat.* **39**, 1677–1685 (2018).
- Kalia, S. S. et al. *Genet. Med.* **19**, 249–255 (2017).
- Natarajan, P. et al. *Sci. Transl. Med.* **8**, 364ra151 (2016).
- Manickam, K. et al. *JAMA Netw. Open* **1**, e182140 (2018).

## Competing interests

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