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[1,2]. 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[1], 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)[3]. 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[4]. 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[5].

More recently, ongoing efforts from the Clinical Genome Resource Actionability Working Group have highlighted over 150 medically actionable genetic conditions[2]. 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 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. ❐

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*[a,b], *KCNQ1*[a,b], *RYR2*[a,b], *SCN5A*[a,b]
	G6PD deficiency	*G6PD*
	Malignant hyperthermia susceptibility	*CACNA1S*[a,b], *RYR1*[a,b]
Conditions that cause reversible metabolic or thrombotic crises that are often induced by severe illnesses	Urea cycle disorders	*ASL*, *ASS1*, *CPS1*, *NAGS*, *OTC*[a,b], *SLC25A13*[b], *SLC25A15*
	Lysinuric protein intolerance	*SLC7A7*
	Fatty acid oxidation disorders	*ACADM*, *ACADVL*[b], *CPT2*, *ETFA*, *ETFB*, *ETFDH*
	Acute porphyrias	*CPOX*, *HMBS*[b], *PPOX*
	Adrenal insufficiency disorders	*AAAS*, *ABCD1*[b], *AIRE*, *LHX4*, *PCSK1*, *PROP1*
	Hereditary thrombophilia	*PROC*[b], *PROS1*[b], *SERPINC1*
	Methylmalonic acidemia	*MMACHC*[b], *MMADHC*[b]
	Atypical hemolytic uremic syndrome	*C3*, *CD46*, *CFB*, *CFH*, *CFI*
Conditions that cause reversible cardiopulmonary complications that can be exacerbated during severe illnesses	Familial cardiomyopathies	*ACTC1*[a,b], *DSC2*[a,b], *DSG2*[a,b], *DSP*[a,b], *LMNA*[a,b], *MYBPC3*[a,b], *MYH7*[a,b], *MYL2*[a,b], *MYL3*[a,b], *PKP2*[a,b], *PRKAG2*[a,b], *TMEM43*[a,b], *TNNI3*[a,b], *TNNT2*[a,b], *TPM1*[a,b], *TTN*
	Cystic fibrosis	*CFTR*
	Refsum disease	*PEX7*, *PHYH*
	Familial pulmonary hypertension	*BMPR2*[b]
	Congenital myasthenic syndrome	*CHRNA1*, *CHRNB1*, *CHRND*, *CHRNE*, *COLQ*, *CHAT*, *GFPT1*, *MUSK*, *DOK7*, *RAPSN*

[a]ACMG59 actionable gene. [b]Clinical Genome Resource actionable gene.

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References

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

Competing interests

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