Managing actionable secondary findings beyond high-penetrant genes through personalised health surveillance

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Background

Genome-informed prevention holds the promise of improving clinical outcomes among individuals at significant risk for developing a disease with a strong genetic component. Risk-stratified phenotypic surveillance for predictive biomarkers might allow for detection of early disease symptoms. However, in the context of low-penetrance diseases, gathering reliable phenotypic information to facilitate such early detection is challenging, since many at-risk individuals will never develop the disease. Therefore, it is crucial that predictive genetic testing for low-penetrant disorders prioritises those conditions for which simple, minimally invasive, and inexpensive phenotyping methods exist that can accurately detect markers associated with early disease symptoms. Such phenotyping assessments should either be suitable for self-administration in the context of at-home phenotyping, or can feasibly be performed within a routine general health check-up.

Objectives

Prioritisation of actionable genetic disease predispositions based on the accuracy, ease and convenience of phenotyping.

Methods

We have developed a rigorous 100-point-scale scoring scheme for prioritising low penetrance diseases to facilitate long-term risk monitoring and early disease detection (Table 1). A key variable to our scoring scheme is “phenotyping”, that is, the ease and accuracy with which relevant phenotypic markers can be sampled and monitored over time.

Table 1. Scoring matrix used to rank low-penetrant diseases based on their suitability for personalised disease risk monitoring and prevention

Topic	PHS score	3	2	1	0
Disease 25%	Disease severity (taken from ClinGen)	Sudden death	Possible death or major morbidity	Modest morbidity	Minimal or no morbidity
	Genetic prevalence	> 1/1000	> 1/10000 < 1/1000	> 1/100000 < 1/1000	<<
	Clinical prevalence	Much lower than expected	Significantly lower than expected	Somewhat lower than expected	Not lower than expected
	Age at clinical onset	> 40 yr	10 - 40 yr	0 -10 yr	< 0 yr
	Likelihood (taken from ClinGen)	> 40% chance	5 - 39% chance	1 - 4% chance	< 1% chance or unknown
Detection 50%	Phenotypic variability	Very high	High	Low	Uniform manifestation
	Phenotyping	Highly effective and convenient	Moderately effective and convenient	Minimally effective and convenient	Non-effective
Intervention 25%	Non-medical	Highly effective	Moderately effective	Minimally effective	Ineffective/ no intervention
	Medical	Highly effective	Moderately effective	Minimally effective	Ineffective/ no intervention

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Results

Ranking of monogenic diseases according to their actionability in the context of at-home testing and routine general health check-up.

We have applied the scoring scheme to evaluate and rank 23 monogenic disorders characterised by reduced penetrance and variable expressivity. Phenotyping was scored either as "phenotyping at home" (data not shown) or according to phenotyping capabilities widely available in private clinics and prevention centers (Table 2). In the prevention clinics scenario, the scores for the 23 disorders ranged from 44.2 to 91.0, with a mean of 69.7 (median of 70.8). Disorders with the highest scores were familial hypercholesterolemia (91.0), Wilson's disease (89.3) and HFE-mediated hereditary hemochromatosis (87.7), suggesting that preventive trials for these diseases are most appropriate for population-wide implementation.

Table 2. Final ranking of monogenic diseases

	Disease		Total score
1	FH	Familial hypercholesterolemia	91.0
2	WD	Wilson's disease	89.3
3	HH	Hemochromatosis, type 1	87.7
4	AIP	Acute intermittent porphyria	81.8
5	ARV CM	Arrhythmogenic right ventricular cardiomyopathy	78.7
6	OTC	Omithin-Trans-Carbamylase deficiency	77.5
7	CPVT	Catecholaminergic polymorphic ventricular tachycardia	76.7
8	HCM	Familial hypertrophic cardiomyopathy	74.3
9	HCU	Homocystinuria	74.2
10	TPCD	Thrombophilia - PROC	73.8
11	FTAAD	Familial thoracic aortic aneurysms and dissections	71.8
12	HPRT2	Hyperparathyroidism 2	70.8
13	BTD	Biotinidase deficiency	68.7
14	GD	Gaucher disease - Glucocerebrosidase	68.5
15	CCM	Cerebral cavernous malformations	67.5
16	MH	Malignant hyperthermia	65.0
17	LQTS	Long QT syndrome	62.5
18	LS	Lynch syndrome	62.3
19	WT	Wilms tumour	58.5
20	HBOC	Hereditary breast and ovarian cancer	55.0
21	AMN	Adrenoleukodystrophy	52.8
22	GSDV	Glycogen storage disease V (McArdle)	50.3
23	FAP	Familial adenomatous polyposis	44.2

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Discussion

We have shown that by systematically evaluating and ranking medically relevant gene-disease associations, it is possible to prioritise low-penetrance disorders for facilitating long-term personalised health surveillance in an efficient and responsible manner. However, some challenges remain. In particular, it is crucial that healthy individuals are not prematurely "labelled" as patients based solely on a genetic risk that may not result in the disease in the given individual. To avoid this, holistic risk assessment is required, which should incorporate comprehensive phenotype data, alongside genetic variants.

To realise the promise of genome-informed prevention in a cost-efficient way, while minimising the potential harm from reporting genetic risks to healthy individuals, we have developed a solution called "Personalised Health Surveillance" (Figure 1). The core idea behind Personalised Health Surveillance is that genome-sequenced individuals should receive a comprehensive risk assessment by combining both genetic and non-genetic risk factors. Subsequently, individuals can be stratified into risk groups and receive personalised phenotyping recommendations that will be continuously updated to reflect the current risk status of the individuals. These recommendations are generated using algorithms that integrate the knowledge base provided by leading disease experts with the data obtained through continuous targeted phenotyping. Upon detection of early disease signs, appropriate non-medical and medical interventions will be initiated. By emphasising the role of the individual in preventive healthcare, it is our hope that the significant potential of population-scale genome-informed prevention can be realised without recourse to scarce public health resources.

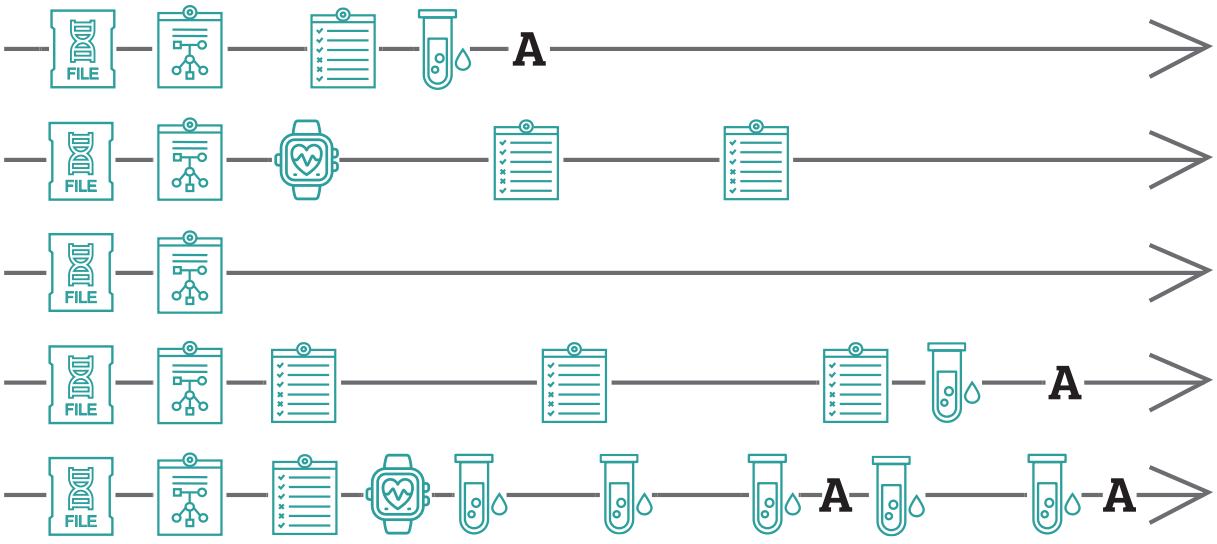

Figure 1. Personalised Health Survaillance

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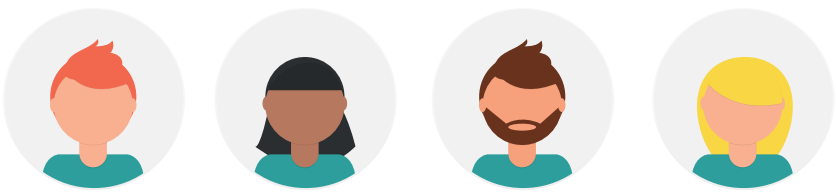

All authors are employees at Megeno S.A.