Comparing the clinical yield of carrier screening: genotyping versus exon sequencing

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Introduction

Expanded carrier screening (ECS) identifies carriers of recessive diseases and may be performed using either targeted genotyping (TG) or next generation sequencing (NGS). The relative efficacy of TG and NGS approaches is incompletely understood and depends on the choice of TG panel, the number of variants interrogated, and the ethnicity profile of the population being studied. Here we present a framework for the systematic comparison of ECS panels and use it to evaluate the performance of several idealized ECS panels.

How to evaluate ECS panels: disease risk

The goal of carrier screening is to identify at-risk couples whose future children might be affected by genetic disease. Previously, carrier frequency (CF) and carrier couple frequency (CCF) have been used to quantify the detection power of ECS panels. However, we recently suggested[1] the use of disease risk (DR) for this purpose, where the disease risk is the probability that a random child will be affected by one of the panel diseases.

Method	Carrier Frequency	Carrier Couple Frequency	Disease Risk
			
Meaning	400 in 10,000 persons are carriers of this disease	16 in 10,000 couples are carrier couples of this disease	4 in 10,000 children will be affected by this disease
Limitations	Cannot compare autosomal and X-linked diseases	Cannot compare diseases with complex inheritance	Harder to compute

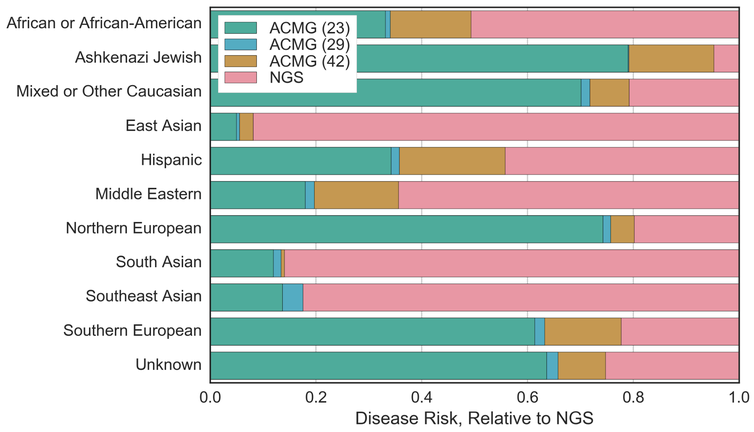
Methods

405,195 patients seeking ECS (*Counsyl Family Prep Screen*) between January 2012 and February 2016 for reason of "Carrier Testing" were anonymized and included in the present analysis. TG and NGS based allele counts were combined to reduce statistical uncertainty[1]. Only diseases considered "Severe" or "Profound", as defined in reference[2], were included for the present analysis. Results for self-reported ethnicities were reweighted based on US census data.

Cohort Summary Statistics	
Patients	**405,195**
Severe / Profound Conditions	**94**
Carriers	**71,785**

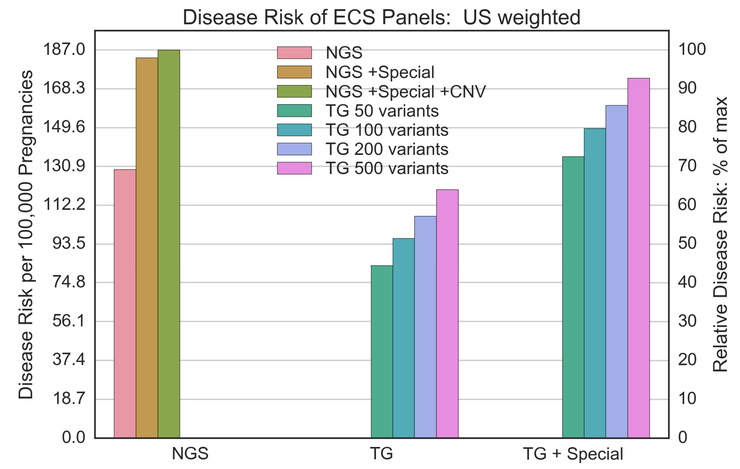
Completeness of CFTR panels

For the specific case of cystic fibrosis, we compared the ACMG-recommended 23, 29 and 42 variant TG panels[3] against full-exon NGS. The small panels perform well for groups with European ancestry, but overlook the majority of DR in other ethnicities, concordant with previous results[4].



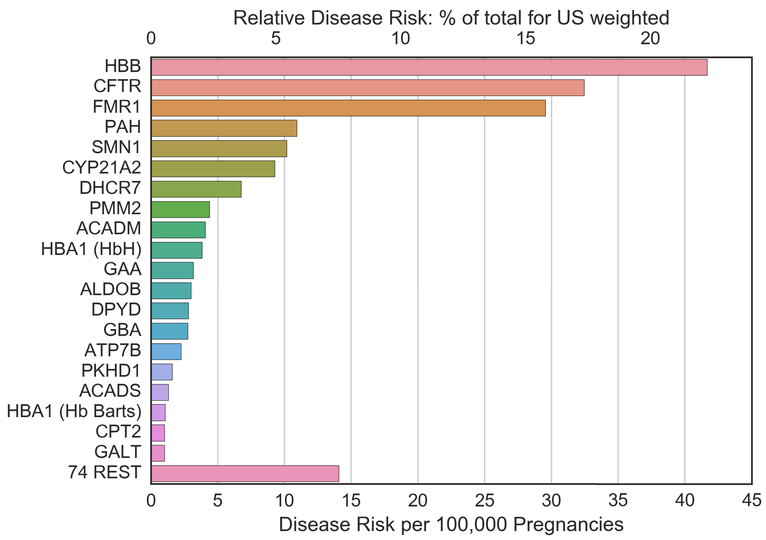
Lessons from idealized panels

To assess the efficacy of various ECS approaches, we compared several idealized ECS panels. We first considered an NGS panel that excludes several special cases (fragile X syndrome, 21-hydroxylase-deficient congenital adrenal hyperplasia, alpha thalassemia, and spinal muscular atrophy) that are difficult to probe for various reasons. We then considered the effect of adding special cases and panel-wide copy number (CNV) calling. We finally considered "best-possible" TG panels with a fixed number of variants, both with and without the special cases. The detection power of each idealized panel shows that neglecting special cases and exon-wide coverage overlooks 10% to 60% of affected children.



High-prevalence genes dominate disease risk

A common question is whether an ECS panel would benefit from the addition of more genes. While adding more genes always improves the detection power, typically the most prevalent diseases contribute over half of the detection power. Thus, the way to improve ECS testing may be to improve sensitivity in existing diseases, such as via panel-wide CNV calling, which (as shown in the previous section) contributes approximately 4 affected children per 100,000.



Disease risk for severe and profound diseases allows systematic comparison of ECS panel detection power. The disease risk of idealized ECS panels shows that high detection rates are primarily determined by special cases and exon-wide coverage.

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