Reproductive carrier screening to identify couples at risk of having children with autosomal recessive and X-linked conditions

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Introduction

The purpose of reproductive carrier screening (RCS) is to identify couples at high risk of having a child with a severe, early-onset and fully penetrant autosomal recessive (AR) or X-linked (XL) disorder, allowing them to make informed reproductive decisions. We have seen an increasing demand for both the basic '3-gene' RCS for cystic fibrosis, spinal muscular atrophy and fragile X, and for an expanded screen of 402 genes (Beacon screen) (see Figure 1). The utility of RCS is best measured by the frequency of couples identified at a high reproductive risk. RCS with an expanded list of genes has greater utility than with just 3 genes,[1,4,5] but the utility of different gene lists will vary with the ethnic mix in the population. In June 2022, the American College of Medical Genetic and Genomics (ACMG) provided a recommended gene list, however, its relevance in the Australian population is uncertain. There is no comparable guideline in Australia, and it is expected that local experience and a national reproductive carrier screening research study, Mackenzie's Mission (MM), will inform the development of such guidelines.

Aim

Compare the potential utility of Beacon, ACMG and MM gene lists in an Australian cohort.

Methods

We analysed 348 AR/54 XL genes (Beacon expanded RCS panel) from 1,624 females and 1,100 males, to determine whether the ACMG-recommended approach would have identified all at-risk couples identified by Beacon. We performed a direct comparison of our panel to the ACMG and MM gene lists in order to determine if any improvements could be made to the current expanded panel available via Sonic Genetics.

Results

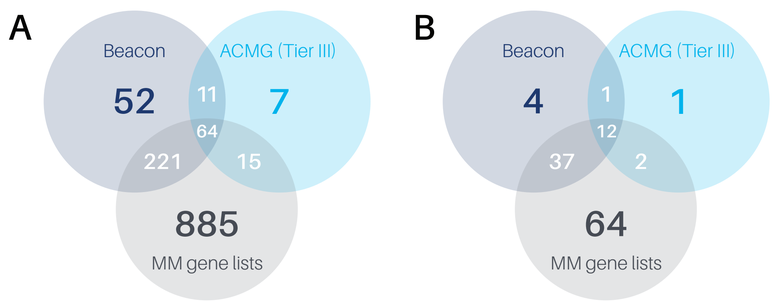

Figure 2: Number of genes covered by three different RCS lists (Beacon, ACMG-recommended and MM gene lists) for AR (A) and XL (B) conditions.

Discussion

Beacon versus ACMG

Analysis of genes in common (75 AR/13 XL) identified 15/887 couples and 10/1624 women at high reproductive risk for an AR or XL disorder, respectively (total 2.3%). Inclusion of additional 314 non-ACMG genes increased the yield of actionable high-risk results by identifying an additional 5 couples and 3 women at high-risk of an AR or XL disorder, respectively (total 3.1%) (see Figure 3). Examples of conditions that would have been missed by the ACMG-approach alone are listed in Table 1.

Beacon versus MM

An additional 63 AR/3XL genes were covered by Beacon panel and gene lists (no additional actionable high-risk results were identified in these genes). The reasons for this included technical limitations inherent to the MM gene lists (such as inability to detect deletional variants in the HBA1/2 or DMD genes that cause alpha thalassaemia and Duchenne muscular dystrophy, respectively) or MM's exclusion of certain phenotypes (such as deafness, or other conditions potentially associated with less severe phenotypes).

Increasing RCS requests (2019–current)

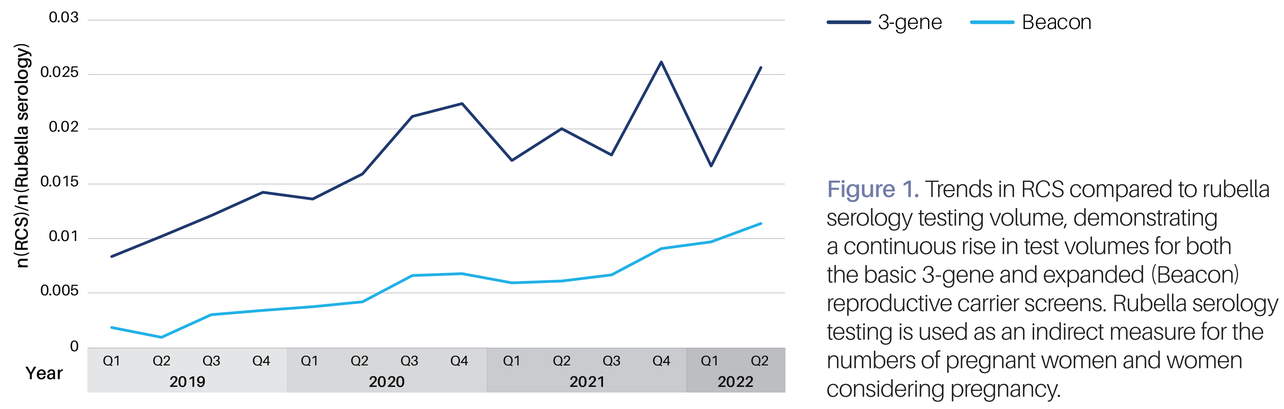

Figure 1. Trends in RCS compared to rubella serology testing volume, demonstrating a continuous rise in test volumes for both the basic 3-gene and expanded (Beacon) reproductive carrier screens. Rubella serology testing is used as an indirect measure for the numbers of pregnant women and women considering pregnancy.

Beacon gene list increases the yield of actionable, high-risk results for both AR and XL conditions

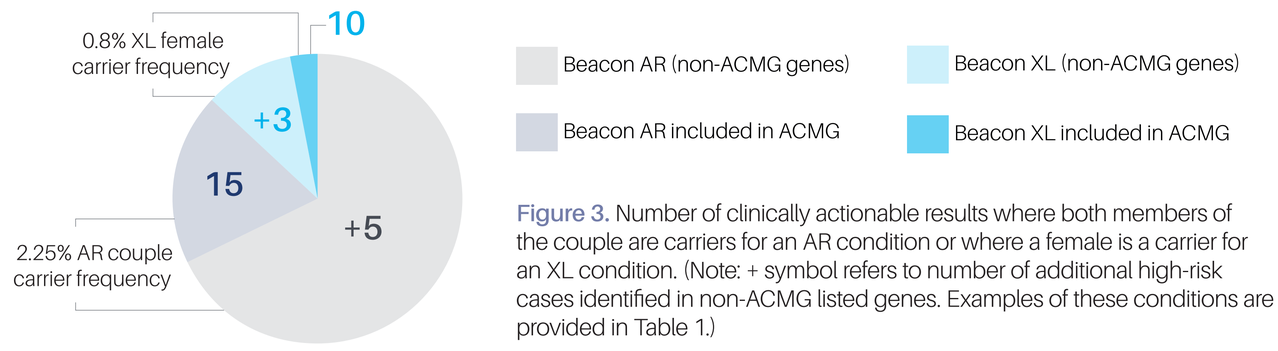

Figure 3. Number of clinically actionable results where both members of the couple are carriers for an AR condition or where a female is a carrier for an XL condition. (Note: + symbol refers to number of additional high-risk cases identified in non-ACMG listed genes. Examples of these conditions are provided in Table 1.)

Table 1. High-risk carriers of severe, early onset AR and XL conditions that would have been missed by the ACMG approach alone, but were identified by the Beacon panel.

Gene	AR/XL	MIM #	Condition	Description
COL4A4	AR	203780	Alport syndrome	Early onset, progressive disorder, characterised by failure to thrive, sensorineural deafness, ocular and renal manifestation and in some cases, progression to end-stage renal failure.
FANCA	AR	227650	Fanconi anaemia	Heterogeneous multisystem disorder that causes genomic instability. Characteristic clinical features include developmental abnormalities in major organ systems, early-onset bone marrow failure, and increased predisposition to cancer.
CHM	XL	303100	Choroideremia	Associated with degeneration of the choriocapillaris, the retinal pigment epithelium, and the photoreceptor of the eye, resulting in progressive vision loss.
EMD	XL	310300	Emery-Dreifuss muscular dystrophy[1]	Early onset degenerative myopathy, characterised by weakness and atrophy of muscle, as well as signs of cardiac involvement and mental retardation.

Conclusions

Our findings show that additional genes beyond the ACMG-recommended list are warranted in the Australian population. Gene content and the detection rate of high reproductive risk are useful metrics in assessing the performance of RCS panels. On the basis of this study, we are revising the next iteration of our expanded RCS panel.

References

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