WMRGL experience of implementing the Illumina TruSight One clinical exome to expand our diagnostic testing of rare diseases.

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Introduction

The Illumina TruSight One clinical exome (TSO CE) was introduced into the West Midlands Regional Genetics laboratory in December 2015 to replace existing next generation sequencing and Sanger sequencing services.

The driving forces behind the change were to expand the test portfolio and increase pick-up rates, whilst maintaining clinical sensitivity and specificity, and reducing costs.

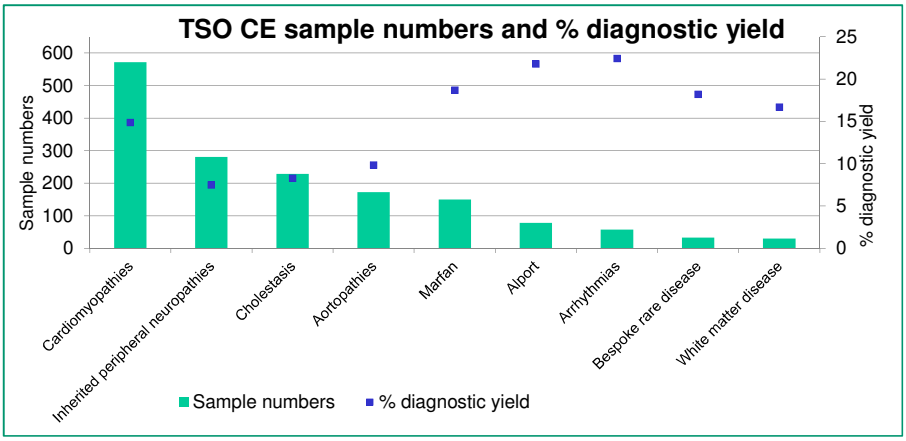
Here we present a review on the first cohort of 1604 cases reported, from a selection of rare diseases services.

Expansion to services following introduction of TSO CE

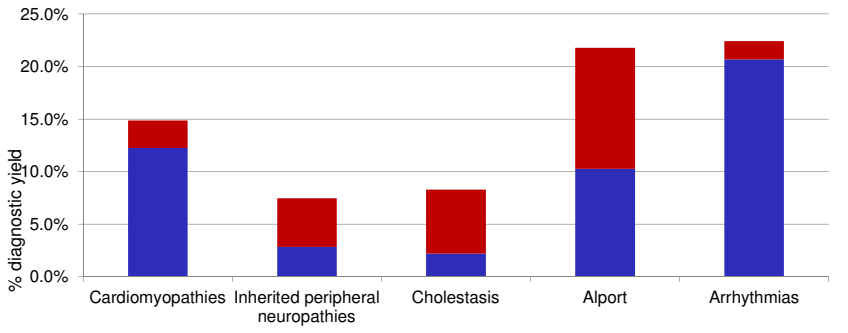
Service	Number of Genes	
	Previous service	TSO service
Cardiomyopathies	4	48 [a]
Inherited peripheral neuropathies	4	62
Cholestasis	4	24 [b]
Aortopathies	N/A	11
Marfan	1	1
Alport	1	3
Arrhythmias	5	25
White matter disease	N/A	34
Bespoke Rare diseases	N/A	Various

[a] ARVC subpanel = 11 genes, DCM = 24 genes, HCM = 18 genes
[b] Two subpanels of 13 and 11 genes

TSO CE sample numbers and % diagnostic yield



Diagnostic Yield Comparison to Previous services



Change to diagnostic yield	1.2x	2.6	3.8X	2.1x	1.08x

% diagnostic yield from genes new to TSO CE service
% diagnostic yield from original genes

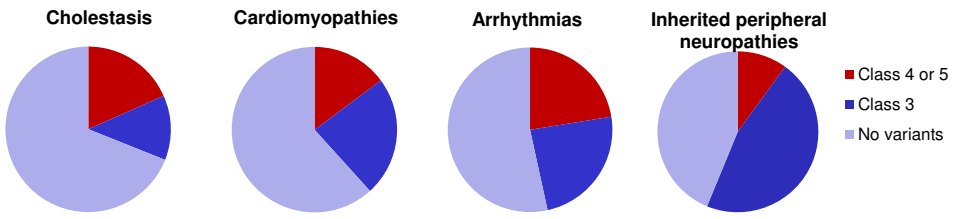
Bespoke TSO CE testing was offered for very rare genes where no alterative testing laboratory was available. The panels analysed for these patients were small (1-3 genes), highly targeted to the patient's phenotype and had an 18.2% diagnostic yield. (see above)

Expansion of services had the greatest impact on diagnostic yield for the inherited peripheral neuropathies (IPN), cholestasis and Alport services. Both IPN and cholestasis are complex disorders which are highly genetically heterogeneous.

Diagnostic yield improvement was more modest for cardiac services. For the cardiomyopathies service, two genes represented nearly ¾ of all diagnoses (MYBPC3 52.9%, n=45; MYH7 21.2%, n=18). This is in line with literature findings for HCM [1], which represents 72.6% of our cardiomyopathies referrals. For the arrhythmia service KCNH2 and KCNQ1 represented 84.6% of diagnoses, which is slightly higher than reports in the literature for long QT syndrome (25%-30% and 30-35% respectively) [2].

Variant interpretation

As a consequence of the expansion to services an increased number of variants requiring classification were unveiled increasing the analysis time required.



Conclusions

- The introduction of TSO CE enabled expansion of diagnostic services resulting in overall increase in diagnostic yield.
- We found that TSO CE can provide flexibility for testing referrals for a range of services while utilising the same laboratory workflow and bioinformatics pipeline.
- We also further employed this process to offer bespoke testing, with minimal additional resource requirements, for very rare genes where no alterative testing laboratory was available.

References

(1) Cirino and Ho, "Hypertrophic cardiomyopathy overview" Gene Reviews, 2014.
(2) Alders, Bikker and Christiaans, "Long QT syndrome" Gene Reviews, 2018.

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