# Genome-wide copy-number detection using a hybrid clinical NGS assay

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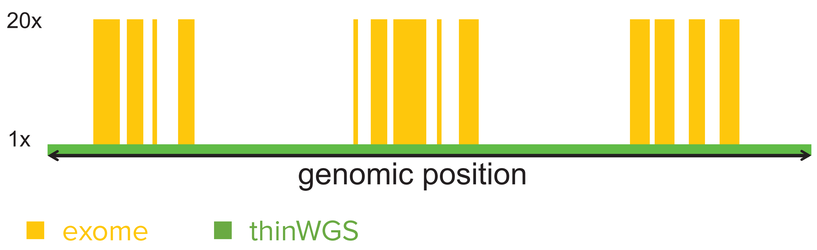
## Overview

Whole-exome sequencing is a cost-effective way of detecting clinically-relevant small variants with high sensitivity. However, targeted assays have limited ability to detect CNVs, because only CNVs that significantly intersect exons can be detected, and in general the breakpoints will not be captured. Until now, clinical NGS tests have employed multiple workflows to reliably capture both the clinical small variants and the CNVs. Here we present a hybrid approach that supplements exome sequencing with thin whole-genome sequencing (thinWGS) in a single clinical NGS workflow.

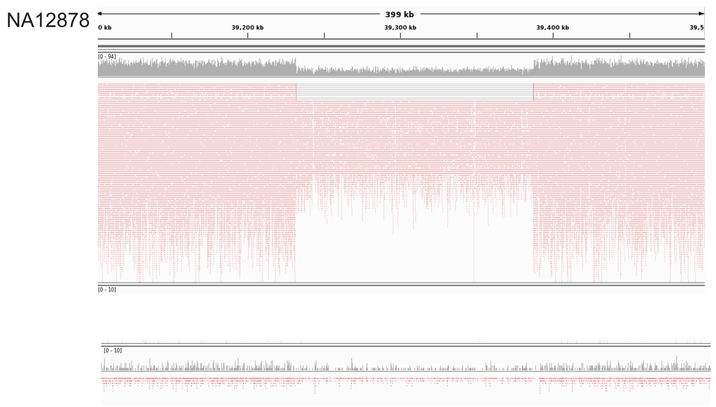
The hybrid clinical assay achieves:

- Clinical-grade small-variant calling on the exome
- Genome-wide sensitivity to large CNVs

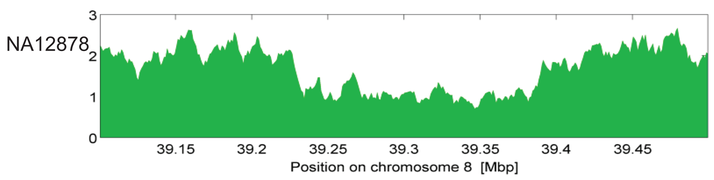



## Methods

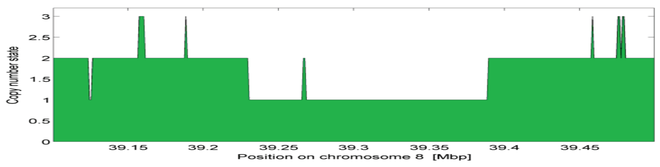
### thinWGS concept



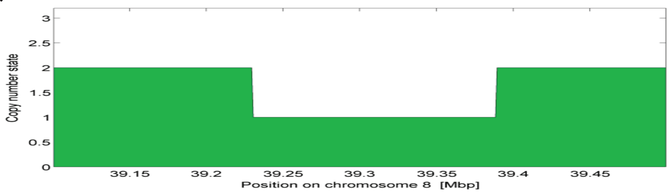

Supplement exome with "thinWGS": a small # of untargeted reads for genome-wide CNV detection.



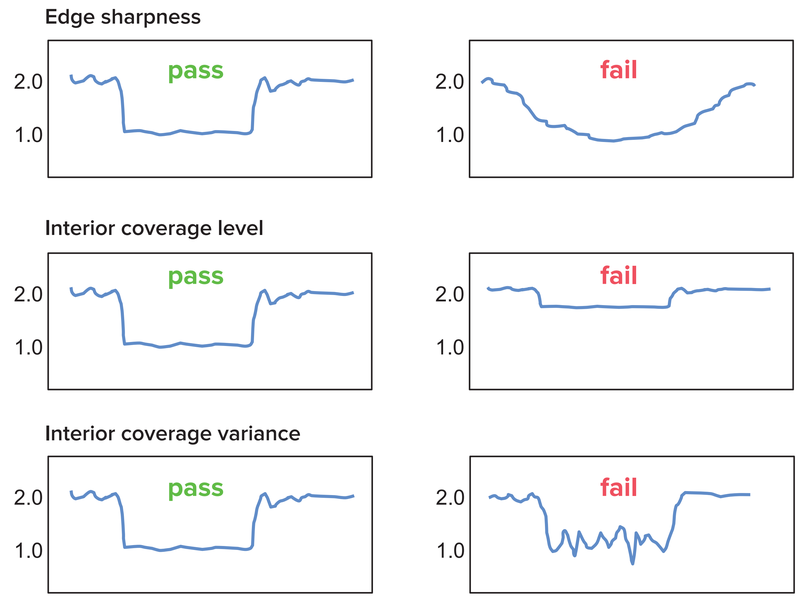

Bin coverage profile to 20 kbp bins to optimize the read-depth signal.




Normalize to reflect local copy number and threshold to get copy-number state.




Apply HMM to remove spurious state changes.




Use morphological annotations to remove false positive calls

### Samples Tested

We evaluated the performance of our thinWGS approach on:

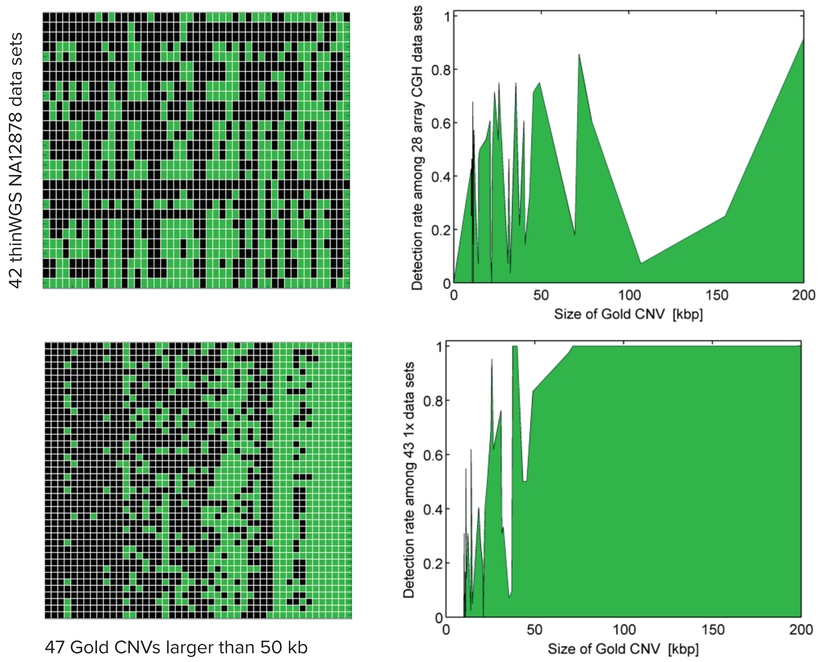
- Coriell samples with known deleterious CNVs
- Personalis/GiaB Gold CNV set for NA12878
- 28 samples for which we have both 60x WGS data and thinWGS data.

## Results

We successfully detected all 29 of the Mbp-scale CNVs in the Coriell samples and achieved ~90% sensitivity for CNVs as small as 60 kbp in the Personalis/GiaB Gold CNV.

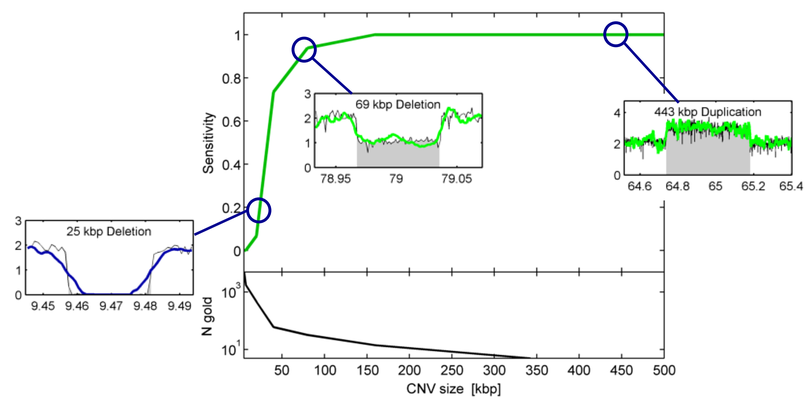
Since the Gold Set is limited to only 7 CNVs larger than 50kb, we developed an expanded set for 28 samples to include more CNVs of this size. The following results are based on our expanded set of 47 CNVs larger than 50kb.

### Comparing thinWGS to array CGH

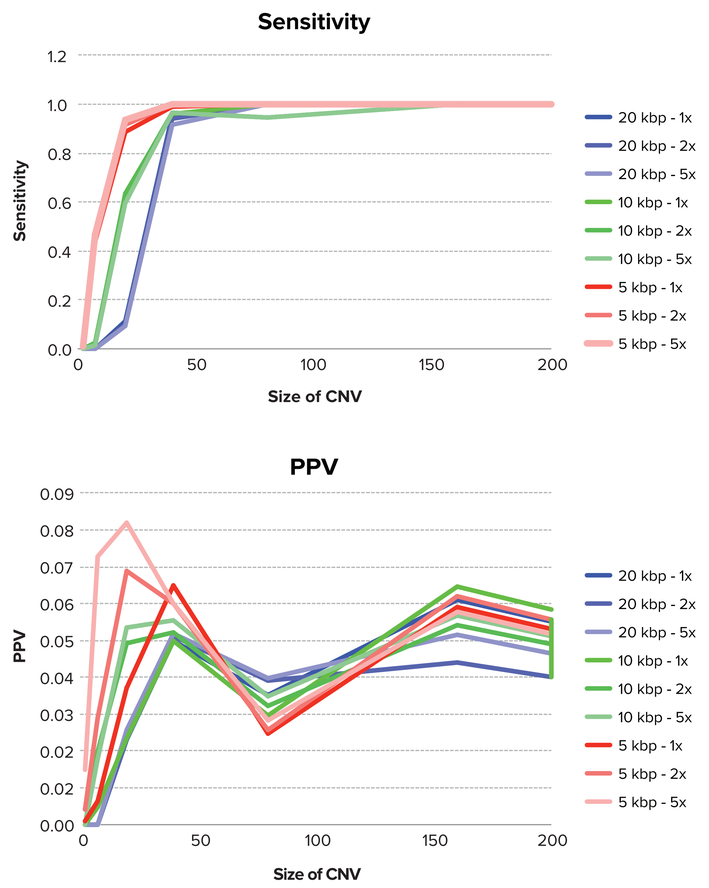



Using a threshold of 75% overlap, thinWGS provides uniform, genome-wide sensitivity to detect CNVs, with 90% sensitivity to features as small as 60 kbp.

### Sensitvity and PPV of thinWGS




Based on our 28-sample CNV Gold sets, our hybrid approach achieves a sensitivity between 90-99% for CNVs greater than 60 kb.




The PPV is lower because of the small number of 'gold' SVs — many of the SVs detected are actually real.

## Conclusion

The Hybrid NGS assay:

- Combines superior sensitivity to clinical small variants with uniform genome-wide sensitivity to large (>=60 kbp) copy-number variants.
- Is far more economical than WGS and therefore a viable clinical diagnostic assay.
- Offers CNV sensitivity that is competitive with many array CGH platforms, in a single NGS assay that simplifies analysis, workflow and lowers turnaround time.

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