INOCRAS

Real-World Applications of WGS Powered by Breakthrough Bioinformatics

Industry Workshop | ASHG 2024

IP109-1124

Introducing our speaker and agenda

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INOCRAS

Real-World Applications of WGS Powered by Breakthrough Bioinformatics

- **WGS-Based Cancer Genomic Profiling:** Precision Insights for Better Outcomes
- **WGS-Based MRD Detection at ppm-Level:** Ultra-Sensitive, Panel-Free Approach
- **Expanding WGS Applications** across Clinical and Research Settings

Introducing Inocras

We focus on **whole genome sequencing** to identify 100% complete genomic makeup and mutations

Our IP protected technology and proprietary bioinformatics pipeline enable us to interpret massive WGS data into actionable insights

We are specialized in **cancer and rare disease**, with more than 13,000 patient cases

Our San Diego Lab is **CAP accredited + CLIA certified**; Seoul Lab is ISO certified

Clinical Laboratory Improvement Amendments

CAP ACCREDITED
COLLEGE of AMERICAN PATHOLOGISTS

HIPAA SEAL OF COMPLIANCE
COMPLIANCY GROUP
HIPAA VERIFIED

Locations

Our partners

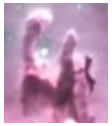
SAMSUNG
HYUNDAI ASAN
SCL 에스씨엘의과학연구소 Seoul Clinical Laboratories
DNAVisit
ULTIMA GENOMICS
WATCHMAKER GENOMICS
MASSIVEBIO

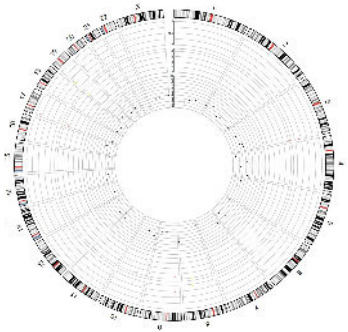
IP109-1124

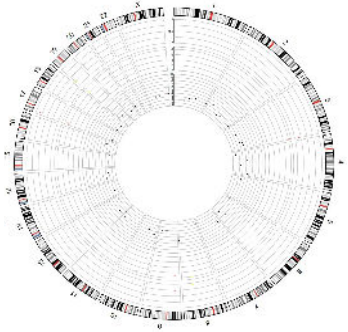
WGS shows the unique genomic profile of individuals

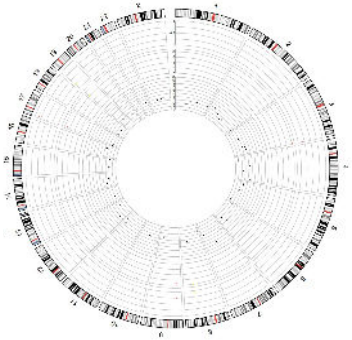
Three different breast cancer patients, cancer mutation profile viewed…

with **1G Targeted Panel** (Foundation Medicine's approach, <0.1% coverage)

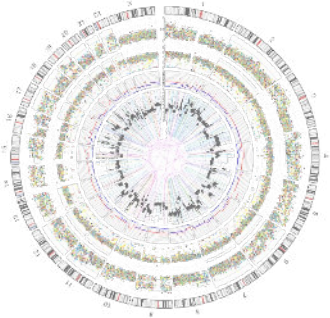




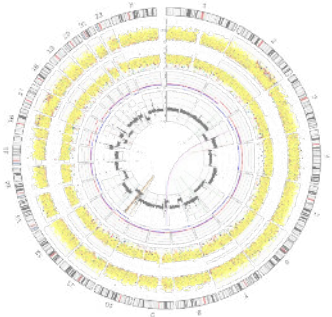




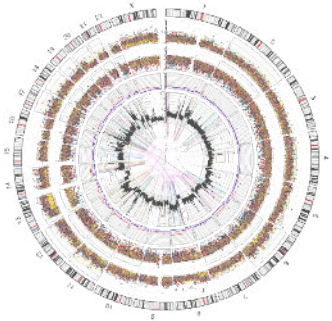
with **3G whole-genome** (Inocras approach, >99% coverage)



F/53, IDC
ER/PR/HER2 (-/-/-)



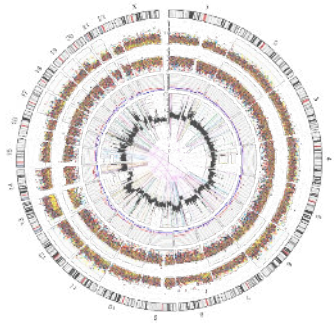
F/50, IDC
ER/PR/HER2 (+/-/-)



F/61, IDC
ER/PR/HER2 (+/+/+)

Note: Data on file

What does this mean clinically?



Inocras' WGS approach

Oncology

~25%

of cancer patients have complicated mutations, often overlooked by conventional TPS /WES tests[1]

Rare disease

20–30%

Additional identification for those who were not previously diagnosed by prior testing (incl. PCR, TPS, WES and ctDNASeq tests)[2]

[1] ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium. Pan-cancer analysis of whole genomes. Nature. 2020 Feb;578(7793):82-93. doi: 10.1038/s41586-020-1969-6.

[2] The increase in diagnostic yield is based on data from a specific sensorineural hearing loss patient cohort and may not be representative of all patient populations. Individual clinical outcomes may vary based on multiple factors

Future is now: By breaking down technology and cost barriers, we provide whole genome insights TODAY

4 myths about WGS	How Inocras's WGS innovations break the status quo
Inaccurate due to lower depth	**Target-Enhanced WGS,** merging benefits of targeted panel (500x depth) + WGS (40x depth for somatic, 20x depth for germline)
Not worth it - limited clinical utility	**User-friendly report,** powered by our proprietary bioinformatics, highlights actionable findings and other clinically relevant findings
Expensive	**Comparable price** with average NGS test price, thanks to high-automation and high-throughput sequencers we are using
Longer time to process	**Turn-around-time (TAT) 14 days** on par with best-in-class testing, thanks to simple workflow and operational excellence

CancerVision: WGS cancer genomic profiling

Our leading technology

- **Proprietary bioinformatics** validated by experts (genome/physician/AI/ computational scientists) and over 13,000 cancer and rare disease WGS cases
- **Target-Enhanced WGS**, merging benefits of targeted panel (500x depth) + WGS (40x depth for somatic, 20x germline)
- **FFPE correction technology (patent protected):** ML model based auto-correction for damaged specimen

More complete genomic test

- **2 in 1:** Somatic + germline paired test
- **Sensitivity/PPV:** >99%[1]
- **Accurate complex somatic variants** (SV, CNV, variants in non-coding areas)
- **Genome-wide mutational pattern** (TMB, MSI, HRD, mutational signatures)
- **Germline** variant detection

All these done within **14 days**

in our **CLIA/CAP lab** in San Diego

at **comparable price** (vs. targeted panel sequencing)

[1] Ferguson, S., Sriram, S., Wallace, J. K., Lee, J., Kim, J. A., Lee, Y., ... Connolly-Strong, E. (2024). Analytical and Clinical Validation of a Target-Enhanced Whole Genome Sequencing-Based Comprehensive Genomic Profiling Test. Cancer Investigation, 42(5), 390–399. https://doi.org/10.1080/07357907.2024.2352438

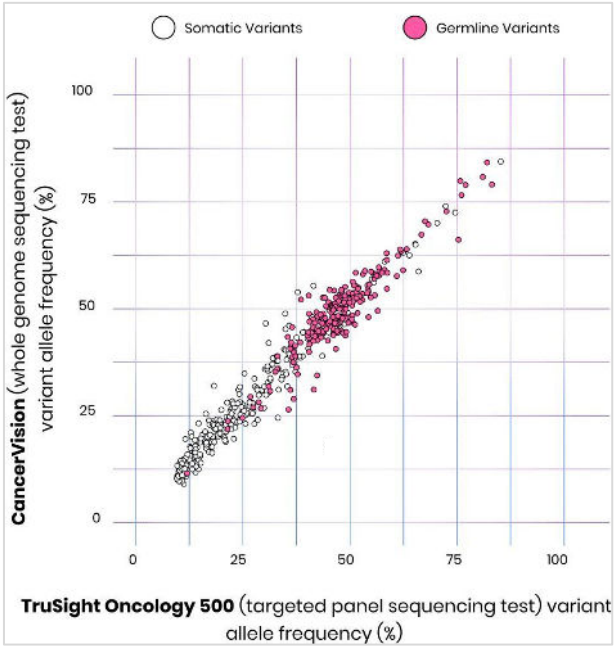
CancerVision: Head-to-head comparison with TSO500; TE-WGS presents additional insights not captured in standard panel sequencing

Objective: Head-to-head comparison between Illumina TSO500 (Standard Panel Sequencing) vs. Inocras CancerVision (TE-WGS)

Prospective observational study (N=49): Routine cancer molecular profiling (TSO 500) was performed on all patients. Then, patients provided peripheral blood samples for DNA extraction, for CancerVision

Results:

- **100% concordance** with TSO500 panel, detecting all 498 variants
- **High correlation in variant allele fraction (VAF)** with TSO500 (r=0.978), demonstrating unmatched accuracy
- **Unique germline vs. somatic detection:** TE-WGS identified 44.8% of shared variants as germline and 55.2% as somatic, offering a complete genomic profile
- **Additional actionable findings:** detected all actionable CNVs from TSO500, plus six additional key deletions missed by TSO500
- **Comprehensive insights into CNVs, gene fusions, MSI, and HRD,** enhancing clinical decision-making



Lee, S et al. Target-Enhanced Whole-Genome Sequencing (TE-WGS) Shows Clinical Validity Equivalent to Commercially Available Targeted Oncology Panel, Cancer Research and Treatment, Sep 2024

CancerVision: Over 70% clinical utility of WGS

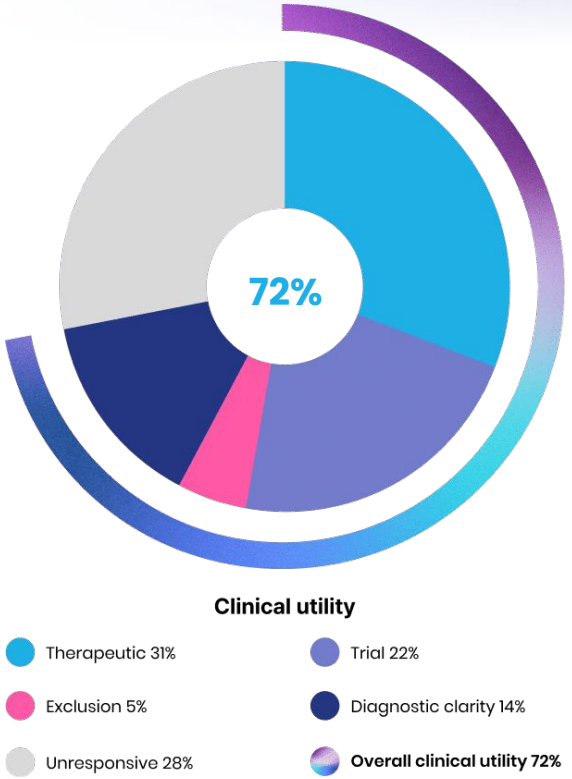
Objective: Assess the clinical utility of TE-WGS (CancerVision) into a real-world hospital setting

Prospective observational study (N = 79): Patients were enrolled by Medical Oncologists. Clinical utility was divided into four distinct subgroups

- Category I-1: informing selection of **targeted therapeutics**
- Category I-2: facilitating the screening for **clinical trials**
- Category I-3: aiding in the **elimination** of potentially ineffective treatment options
- Category II: **clinical clarity**

Results:

- **72% (68/95) of patient reports yielded clinically relevant insights.**
- The mean turnaround time from the sample receipt to the report was 11 business days



Kim, R., Kim, S., Oh, B.BL. et al. Clinical application of whole-genome sequencing of solid tumors for precision oncology. Exp Mol Med 56, 1856–1868 (2024).

CancerVision: More accurate genome-wide markers, reducing false positive significantly

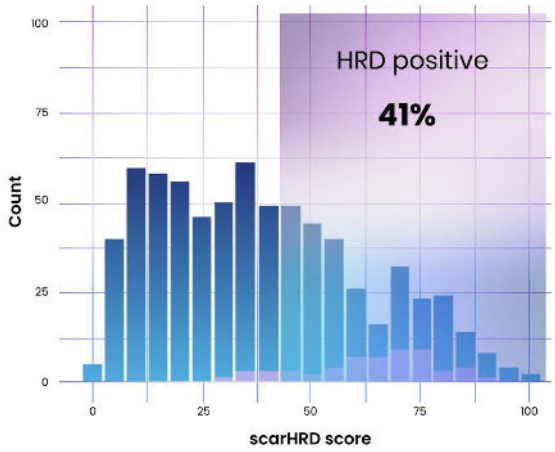
Objective: Assess Homologous Recombination Deficiency (HRD) status in **1,364 breast cancer patients** between standard targeted panel vs CancerVision approaches.

Results:

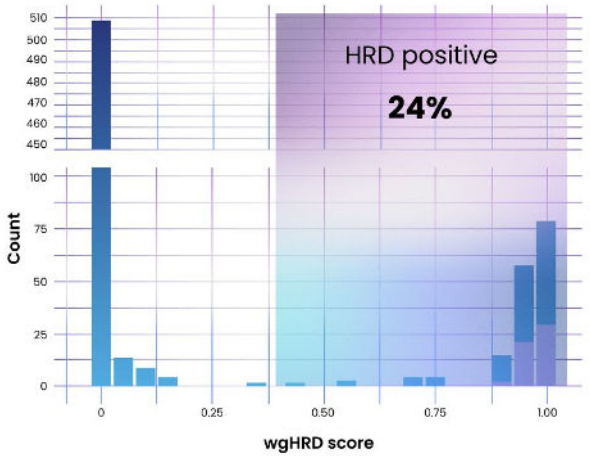
- Standard panel:
  - Contrived cut-off between HRD (+) vs. (-)
  - Elevated risk of false positives
- CancerVision:
  - Clear distinction between HRD (+) vs. (-)

HRD analysis is a part of CancerVision. NOT additional add-on test

Targeted panel (0.03% genome)



Whole-genome (100% genome)



Pre-print - https://doi.org/10.21203/rs.3.rs-5094752/v1

Published

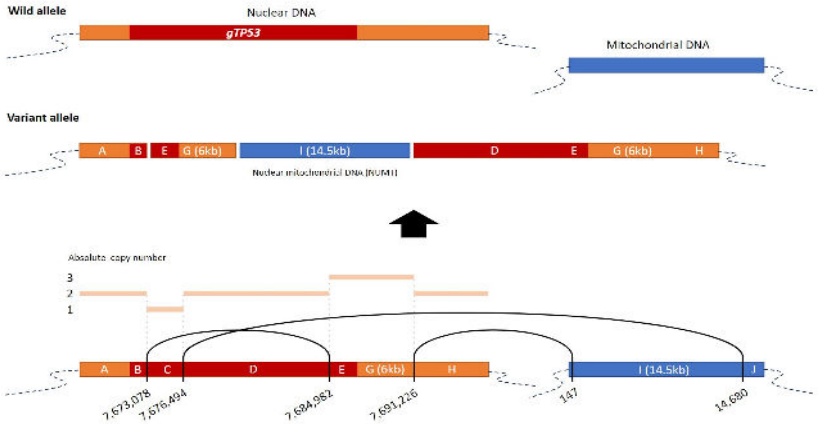
CancerVision patient case: Li-Fraumeni Syndrome

Patient context

- Breast Cancer ER/PR/HER2 (+/-/+)
- History of sarcomas, suggesting multiple primary malignancies
- Neoadjuvant chemotherapy

Inocras solution / insights

- Key driver mutations included **amplification in ERBB2 and PIK3CA**
- **Germline – structurally disrupted TP53:** complex rearrangement involving genomic insertion of nuclear mitochondrial DNA segment (NUMT)



Clinical impact

- **Diagnosed with Li-Fraumeni Syndrome** (linked to TP53), a highly penetrant cancer syndrome associated with a high lifetime risk for cancer
- **Informed ordering of additional hereditary testing in siblings** (also reported the same TP53 variant)

Shin K, et al. Clinical Utility of Whole-Genome Analysis as One-for-All Test for Breast Cancer: A Case Series. Case Rep Oncol. 2024 Feb 23;17(1):317-328 doi: 10.1159/000536087.

MRD**Vision**: WGS MRD detection with one-in-a-million LOD

Cancer**Vision**

TE-WGS cancer profiling

More complete picture of cancer to support diagnosis and treatment selection

MRD**Vision**

Use Cancer Vision** as an input,**

Monitor WGS ctDNA longitudinally

- **WGS approach:** no panel needed
- **Ultra sensitive:** one-in-a-million level LOD
- **Simple workflow,** 2 week TAT
- **50% lower cost** vs. widely used MRD today

Data on file

MRD**Vision**: Whole genome approach, no panel needed

Maximize signal

powered by the **Inocras whole-genome platform**

INOCRAS

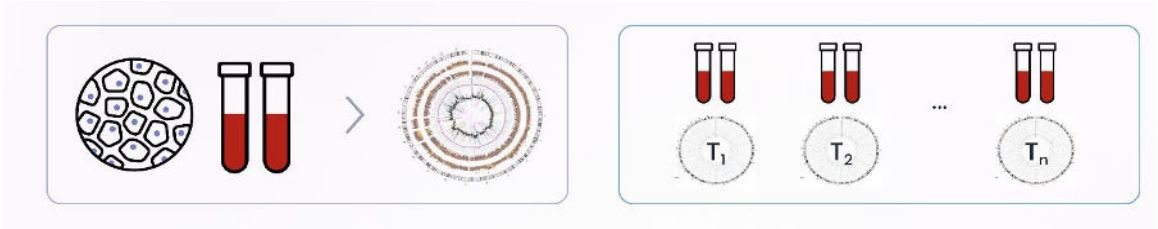
Minimize noise

powered by **Ultima ppmSeq™**

ULTIMA GENOMICS

WGS baseline
Tumor-normal paired whole genome cancer profiling for each patient

ctDNA monitoring
Comparing WGS baseline vs. WGS data in ctDNA



- Cancer**Vision** delivers whole genome cancer profiling, creating individualized WGS tumor somatic signatures as a baseline for each patient.
- MRD**Vision** then utilizes this personalized WGS baseline to detect tumor DNA fraction by analyzing WGS data from cfDNA.
- Ultima Genomics' **ppmSeq™** (paired-plus-minus sequencing) enhances accuracy by concurrently amplifying matching forward and reverse DNA strands on the same bead, achieving ultra low background error rate of 10^{-6}

Data on file

MRD**Vision**: Analytical validation methodology and results

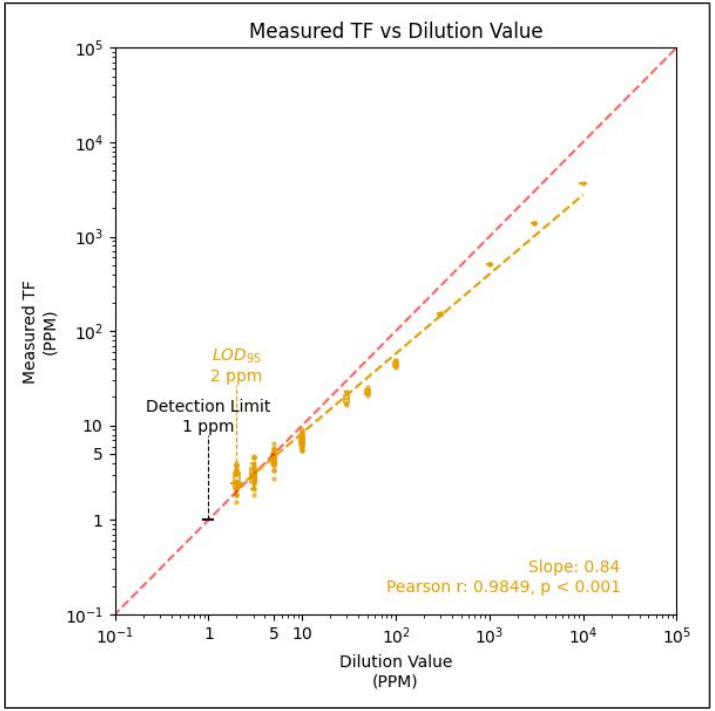
Methodology:

1. **Three tumor and matched-normal cell line pairs:**
   - HCC2218, HCC1395, and NCI-H2126 from American Type Culture Collection
   - Tumor DNAs were diluted into matched-normal DNAs at concentrations ranging from 10^{-2} to 10^{-7}, simulating various levels of circulating tumor DNA
   - Total of 84 ppmSeq experiments

2. **Samples were sequenced using Ultima Genomics ppmSeq**
   - 40x read-depth
   - A mixed (duplex) rate of 33%
   - Absolute error rate of 1.43×10^{-7}

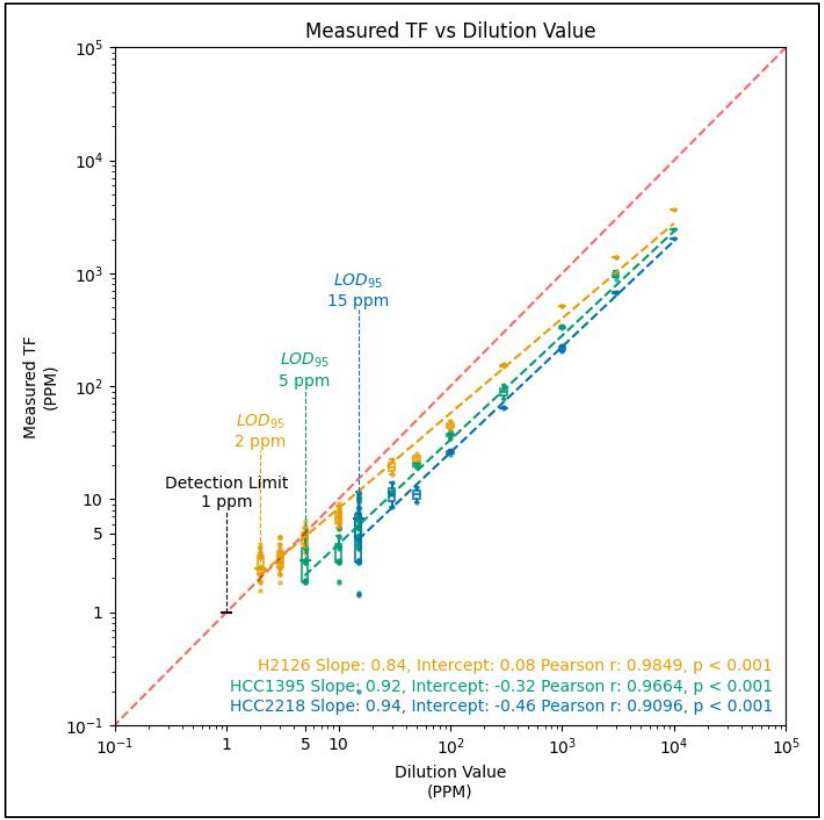
Limit of detection results:

- **Detection threshold (LOD50): 1 ppm**
  The minimum concentration at which a positive result can be reliably called at the defined specificity.
- **95% of Limit of detection (LOD95): as low as 2 ppm**
  At >10,000 mutations, 40x read-depth
  The concentration at which 95% of readings would be positively detected.



Data on file

MRD**Vision**: Ultra-high sensitivity at various tumor burden levels



LOD95 results across three cell lines:

2 ppm from NCI-H2126

- 117,676 SNV out of 169,079 somatic mutations

5 ppm from HCC1395

- 38,829 SNV out of 67,191 somatic mutations

15 ppm from HCC2218

- 23,494 SNV out of 51,350 somatic mutations

Data on file

MRD**Vision** delivers accuracy, affordability, and more WGS data

Key features	Inocras - MRDVision	Widely adopted MRD products
Product concept	Tumor-informed	Tumor-infomed
Genome coverage	**Baseline:** TE-WGS (CancerVision) **ctDNA:** WGS	**Baseline:** WES or WGS-based **ctDNA:** Personalized panel with limited number variants
Technology platform	Inocras WGS Ultima ppmSeq™	Own IP or partnership
LOD	**0.0001%** LOD95: as low as **2 ppm**	Mostly 0.01% - 0.001% A very few has a single digit ppm for LOD95
Deliverable	**WGS ctDNA** monitoring report + **TE-WGS cancer profiling data** (CancerVision)	ctDNA monitoring report
TAT	First order: 4 weeks or less Follow-ups: 2 weeks or less	First order: 4-5 weeks Follow-ups: 7-14 days
Price	**Affordable** (~50% of commercially available products)	High cost due to high read depth of personalized panels

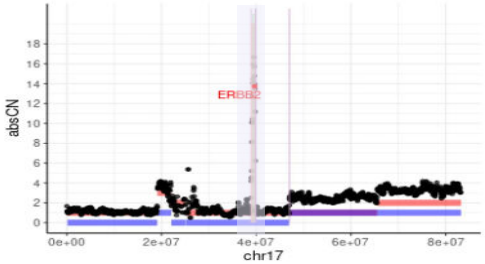
Talk to our representatives on MRDVision launch package offer at ASHG

Data on file

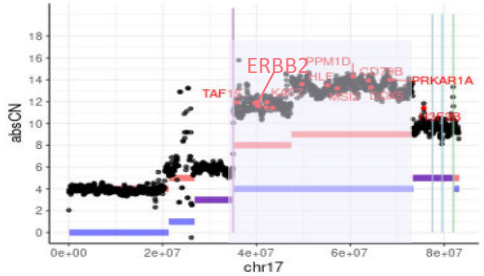
Expanding WGS applications - HER-2 focal vs. broad amplification

HER-2 amplification – FOCAL vs. BROAD

HER-2 **FOCAL** amplification



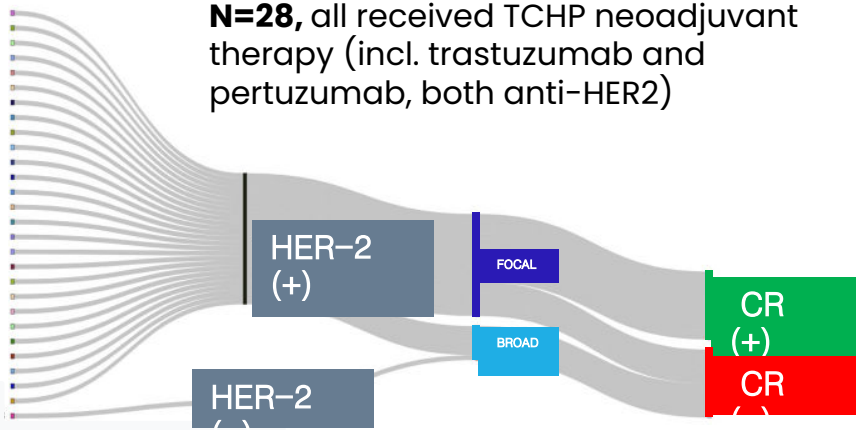
HER-2 **BROAD** amplification



Distinction between FOCAL vs. BROAD is only possible with WGS (CancerVision)

Drug response to anti HER-2

N=28, all received TCHP neoadjuvant therapy (incl. trastuzumab and pertuzumab, both anti-HER2)



Complete remission rate after TCHP therapy:

- HER-2 FOCAL amplification 66%
- HER-2 BROAD amplification 0%

Data on file

RareVision: WGS-based Rare disease diagnosis

- **Rare disease** pathogenic variant diagnosis
- **Whole-genome-sequencing** (30x)
  - Comprehensive analysis
  - Structural variants, copy number variants
- Genes associated with **5,000+ rare diseases**
- **ACMG/ClinGen** guideline and standards
- **Evidence**:
  - **23.6% add'l diagnosis** among patients who were not previously diagnosed with other genetic tests (from ~400 hearing loss cohort)
  - **31.2% overall diagnosis rate**, from previously undiagnosed rare disease patient cohort (from 5,000+ samples)
- **Sample type –** Buccal, Saliva, Blood
- **Turnaround time** 14 days or less

RareVision

John Smith
Patient ID: H23/028662

Patient
Name: John Smith
Patient ID: H23/028662
Sex at birth: Male
Date of birth: Nov 20, 1987

Physician
Name: John Doe
Institution:
Heritage Medical Center
Contact: +82-10-0000-0000
Address:
1600 Amphitheatre Parkway, Mountain View, CA 94043

Specimen
Specimen ID: C346399(9)
Specimen type: Blood
Specimen collection:
Blood draw
Collected: Nov 20, 2023, 11:23
Received: Nov 24, 2023, 13:20
Clinical diagnosis:
Autism spectrum disorder

Test Information
Test name:
Whole genome analysis and interpretation
Quality: Satisfactory
Sequencing mean depth:
48.2x

RESULT SUMMARY

Positive variants detected	*PTEN*
Inconclusive variants detected	*SCN2A, TCF7L2*
Secondary (incidental) findings detected	*BRCA1*

A. POSITIVE VARIANTS

Gene	Variant type	Zygosity	ACMG classification	Related diseases
PTEN	SNV	Heterozygosity	Likely pathogenic	Lhermitte-Duclos disease

B. INCONCLUSIVE VARIANTS

Gene	Variant type	Zygosity	ACMG classification	Related diseases
SCN2A	SNV	Heterozygosity	Pathogenic	Developmental and epileptic encephalopathy 11
TCF7L2	SV	Heterozygosity	-	Diabetes mellitus, type 2, susceptibility to

C. SECONDARY (INCIDENTAL) FINDING

Gene	Variant type	Zygosity	ACMG classification	Related diseases
BRCA2	SNV	Heterozygosity	Likely pathogenic	Breast-ovarian cancer, familial, 2

D. INTERPRETATION

- In *PTEN*, variant ENSP00000278317.6:p.R234H is detected as likely pathogenic, and the variant is identified as heterozygous. And the variant is identified as de novo.
- *PTEN* is known to be associated with the following diseases.
  Lhermitte-Duclos disease (Autosomal dominant) (PMID : 24102544, 21926107).
- Incidentally, in *BRCA2*, variant ENSP00000262426.4:p.F85L is detected as likely pathogenic, and the variant is identified as heterozygous. And the variant is identified as de novo.
- *BRCA2* is known to be associated with the following diseases.
  Breast-ovarian cancer, familial, 2 (Autosomal dominant) (PMID: 17924331).
- Geneticist evaluation for clinical correlation of these results is recommended.

*SNV; Single nucleotide variant, INDEL; Insertion and deletion, SV; Structural variation, TE; Transposable elements, DEL; Deletion, DUP; Duplication, INV; Inversion, BND; Translocation, Chr; Chromosome, AD; Autosomal dominant, AR,Autosomal recessive; XR, X-linked recessive

Data on file

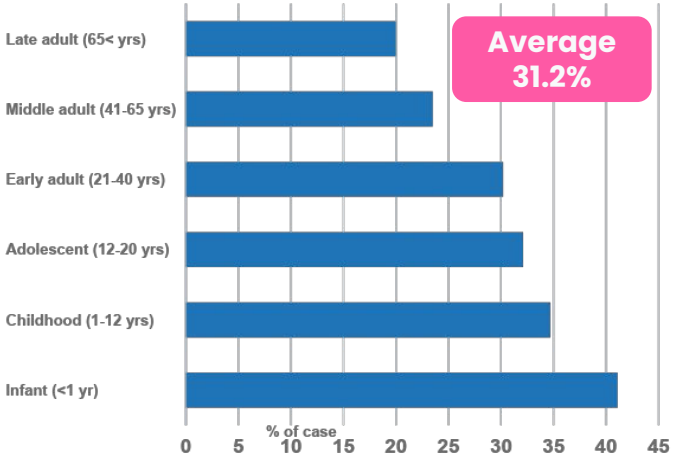
RareVision: National Project of Bio Big Data

Objective: Identify causative pathogenic variants for rare disease patients and their family members

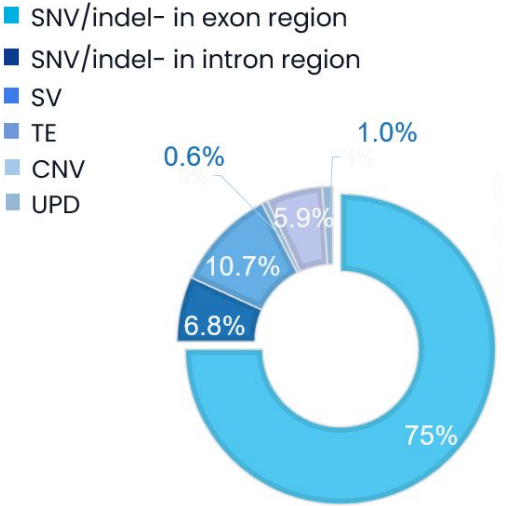
Results:

- **In 31.2% of cases** (683/2,188), a causative pathogenic variant was detected.
- **Benefits of WGS:** 784 pathogenic variants were identified across the study. Among them…
  - **6.8% of SNVs** in intron regions, not captured by WES
  - **10.7% SVs, 5.9% CNVs** - often not accurately captured in WES

% of cases identified with causative pathogenic variants (N = 2,188)



Variant Classification (N = 784)



Data on file; SV = structural variations, TE= Transposable Elements, CNV = copy number variations, UPD= Uniparental Disomy

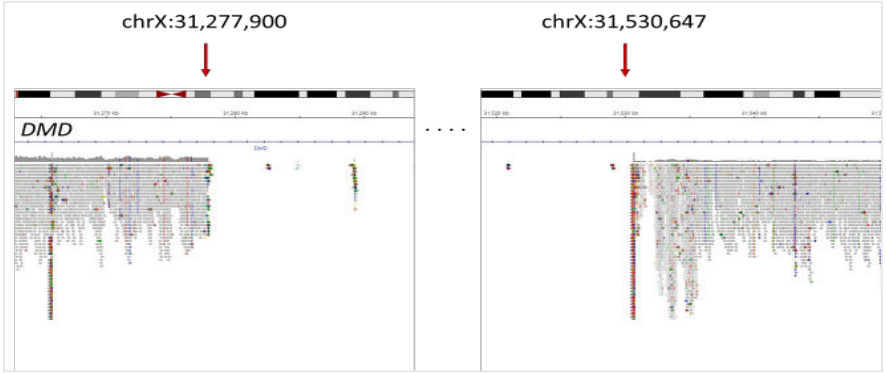
RareVision patient case: Duchenne Muscular Dystrophy

Context:

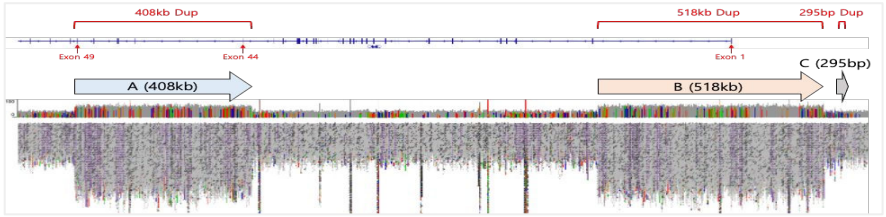
One childhood and one adolescent-aged males presented with progressive muscle weakness.

RareVision was ordered for each patient

Large Deletion



Complex rearrangement



Clinical impact

- **Complex structural mutations identified** that could not be detected through targeted panels or WES
- **Diagnosed with Duchenne Muscular Dystrophy**

Our Whole Genome assay list

CancerVision

Cancer genomic profiling, for personalized diagnosis

MRDVision

WGS-informed MRD, no personalized panel needed

HerediCaVision

Hereditary cancer risk screening test for family members

RareVision

Rare disease pathogenic variant diagnosis

ASDVision

Autism spectrum disorder diagnosis support

CareVision

Health and disease risk screening test

CAP/CLIA assay

Currently RUO available
CAP/CLIA from Q4 2024

Currently RUO available

Introducing research service line

WGS within 14 days

- Somatic and germline WGS
- Latest **Illumina** (Novaseq X+) and **Ultima** (UG100)
- Ultima's commercial lab partner
- TAT: **14 days**

World class bioinformatics

- **Proprietary,** automated bioinformatics
- Automated secondary analysis
- **Curation and annotation** by Inocras genome scientists

CAP / CLIA lab

- Serving both **clinical and research needs** and supporting FDA submissions for Phase II & III clinical trials.
- **Custom assay** development is also available.

Customized solutions

- **Customized to meet researchers need:** Perform sequencing only, sequencing + curation, standardized or customized reports
- **Advisory services** upon your request

Committed to medical and science

- **30+ collaborative research** studies with academia and pharma
- 1,300+ breast cancer patient cohort

  500+ liver cancer patient cohort

  300+ hearing loss patient cohort

Customers / Collaborators

The Jackson Laboratory
Shriners Children's
ULTIMA GENOMICS
AstraZeneca
BOUNDLESS BIO
ASAN Medical Center
SAMSUNG MEDICAL CENTER
SNUH
SEVERANCE HOSPITAL
THE CATHOLIC UNIVERSITY OF KOREA SEOUL ST. MARY'S HOSPITAL

Customizable whole genome data and insight generation for research projects

Sequencing

- High quality in CLIA-certified, CAP-accredited lab
- With or without DNA extraction and library prep
- Latest sequencers – Novaseq X+, Ultima UG100
- Flexible raw data files (typically FASTQ, BAM, CRAM)

Bioinformatics

- World-class bioinformatics providing WGS insights
- Analytics, interpretation, and/or report generation
- Curated data files (typically VCF) or Inocras Dx reports
- Customized report available depending on volume

Sequencing only

Bioinformatics only

End-to-end services

Expert advisory support

Our team of MDs and PhDs specialize in medical, genomic science, computer science and bioinformatics and provide expert advisory services for your projects

Pharma / biotech research service examples

Example services	Select collaborations we have worked on	
Finding new biomarkers or targets	Breast cancer	Phase II clinical and exploratory biomarker study for advanced breast cancer patients with homologous recombination deficiency
	Lung cancer	Phase III, open-label study with stage IV non-squamous NSCLC with activating EGFR mutation or ALK translocation
Clinical trial patient screening	Oncogene amplification cancers	Phase I/II, WGS supported patient screening for characterization and retrospective testing to develop ecDNA-directed therapies (ecDTx)
Treatment responses	Solid tumor	Phase IV, PARPi treatment responses in advanced solid tumor patients with homologous recombination deficiency identified by whole genome sequencing
Commercial patient identification	Rare disease	Patient screening tool for rare disease patients with non-classical mutation profile, previously undiagnosed or unconfirmed for drug treatment