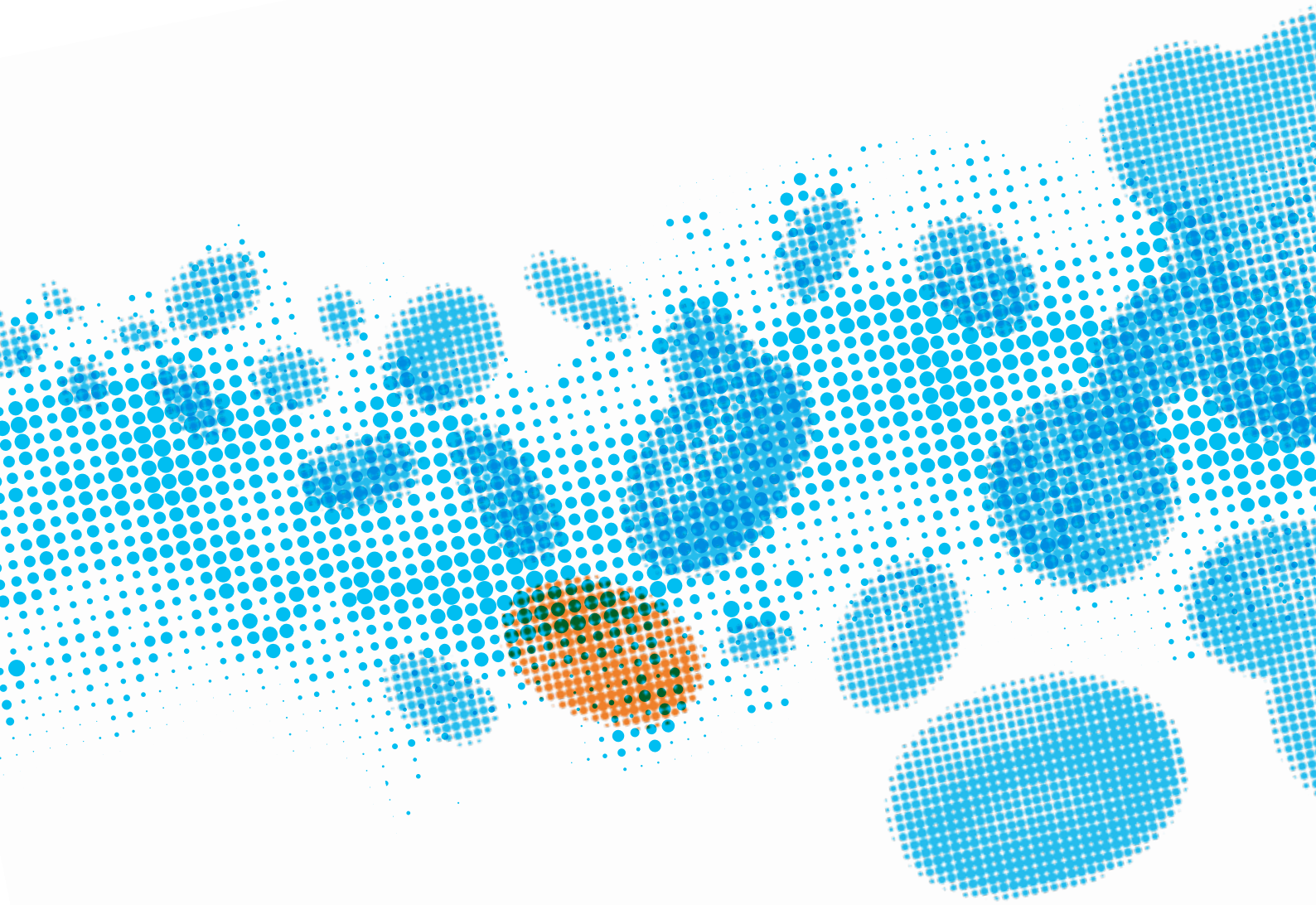
Prima Cancer Genetics

MEDGENOME

NGS-based Imatinib Resistance Mutation Analysis

- Higher Sensitivity
- Enhanced Accuracy
- Earlier Detection



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Chronic Myeloid Leukemia & Imatinib

Chronic Myeloid Leukemia (CML)

- CML accounts for 15%-20% of all adult leukemia.
- The Philadelphia Chromosome results in the fusion of N-terminal region of BCR gene with the C-terminal kinase domain of ABL1 gene.
- This produces a constitutively active chimeric protein kinase responsible for leukemogenesis in CML.

Imatinib

- Response to Imatinib is better than other available therapies and presents fewer side effects.
- Major challenge is development of resistance over a period of time.
- Most common resistance due to mutations in the ABL1 kinase domain.

Imatinib resistance

- Over 130 mutations reported in Imatinib resistance patients.[1-4]
- Clinical intervention depends on mutation presence.

3 alternatives

Increase in Imatinib dose	Switching to second generation inhibitors	Alternate treatment options

- The T315I mutation appears to confer resistance to multiple targeted tyrosine kinase inhibitors.
- Other mutations may be more responsive to other therapies.[1]

Test details

MedGenome offers	Sample requirements	Required forms	Test Code
Imatinib Resistance Mutation Testing by NGS	 Minimum of 3mL of peripheral blood OR  EDTA anticoagulated peripheral blood or 1µg of RNA	Test requisition form along with relevant clinical information including pedigree, consanguinity, age of onset, clinical presentation and symptoms	MGM198

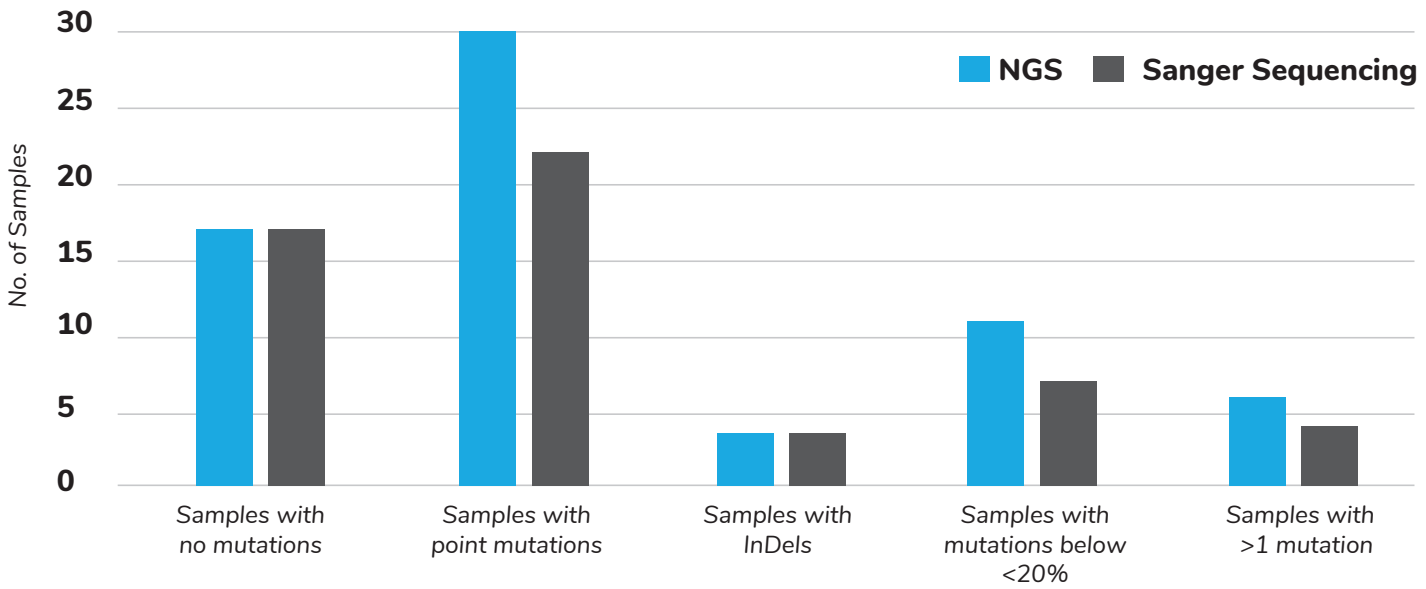
NGS-based analysis

- Complete characterization of the spectrum of minor (<20%) mutated variants.
- The ability to follow the dynamics of resistant mutations over time.
- Reconstruction of the clonal architecture of mutated populations, in the case of multiple mutations, occurring within the same amplicon.
- Early detection with high sensitivity.
- Reliable detection of emerging BCR-ABL1 mutations.
- The ability to detect all resistant mutations and not just hotspots

Assay characteristics	NGS	Sanger Sequencing	Real time - PCR (RT-PCR)
Throughput	High	Low	Medium
Sensitivity of mutation detection (LOD)	>1%	>20%	>5%
Ability to detect novel mutations	Yes	Yes	No
Identification of InDels	Yes	Yes	Yes
Distinguish between compound mutations	Yes	No	No
Identification of Polyclonal mutation	Yes	No	No
Quantification of mutation burden	Yes	No	No

NGS vs Sanger Sequencing for IRMA

Comparison statistics of Imatinib Resistance Mutation Analysis performed on 47 paired samples by NGS and Sanger sequencing



Validation results

Sample type	Mutation type	Sensitivity	Specificity	Accuracy	Limit of Detection
Peripheral blood RNA	SNV / Short-Indels	100%	100%	100%	≥1%

References:

1. Soverini, Simona, et al. "Bcr-Abl kinase domain mutation analysis in chronic myeloid leukemia patients treated with tyrosine kinase inihibitors: recommendations from an expert panel on behalf of European LeukemiaNet. " Blood (2011): blood-2010.
2. Gorre, Mercedes E., et al. "Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification." Science 293.5531 (2001): 876-880.
3. Chaitanya, Puligundla Krishna, et al. "The role of mutation testing in patients with chronic myeloid leukemia in chronic phase after imatinib failure and their outcomes after treatment modification: Single-institutional experience over 13 years." Indian journal of medical and paediatric oncology: official journal of Indian Society of Medical & Paediatric Oncology 38.3 (2017): 328.
4. Nardi, Valentina, Mohammad Azam, and George Q. Daley. "Mechanisms and implications of imatinib resistance mutations in BCR-ABL." Current opinion in hematology 11.1 (2004): 35-43.

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Get in touch

1800 103 3691

diagnostics@medgenome.com

medgenome.com