Genexus News

Issue: February 28

Featured Publication

Democratizing The Future of Precision Medicine

Faye Nourollahi, February 7, 2020, *Clinical Omics*

The chip used in the Genexus system is designed to run smaller batches, a key consideration for health systems that want to deliver results quickly but do not generate a high volume of tests.

...Outsourcing next-generation sequencing (NGS) testing can be very expensive, and stringent sample requirements often lead to poor or inconclusive results. Recent clinical research studies show this issue affects approximately 20% of patients, excluding samples not submitted because they failed to meet sample quantity criteria. A study published in the journal Clinical Lung Cancer underscores the logistical challenges that limit local hospitals from providing NGS-based genomic testing, even though most patients are treated in a local setting. These NGS adoption barriers—including coordination of sample handling, cost, product complexity, long turnaround times, insufficient amounts of tissue—must be addressed if the healthcare industry is serious about advancing precision medicine. These factors often result in the majority of local molecular laboratories relying on limited single-gene tests or sending out samples for testing. Frequently, the treating oncologist is unaware which genes, or biomarkers, to test for due to the fast pace of new discoveries about the genetic influences on disease, and targeted therapies becoming increasingly unique to certain mutations in patient populations. But some companies are aiming to make genomic analysis for patients more accessible and easier to order for community oncologists in the future, including Thermo Fisher Scientific and Contextual Genomics. Thermo Fisher has developed a tool that would one day allow a hospital lab to consolidate all genetic testing into a single molecular test. Thermo Fisher announced the launch of its Ion Torrent™ Genexus™ System for research use late last year, it's a fully integrated, NGS platform that features an automated specimen-to-report workflow. Impressively, it can deliver results economically in a single day*, and is designed to enable local labs to adopt NGS testing in house. Thermo Fisher has also introduced the Oncomine™ Precision Assay, an innovative pan-cancer research panel for the Genexus platform, which enables comprehensive genomic profiling from formalin-fixed, paraffin-embedded (FFPE) tissue and liquid biopsy samples with a single assay.

“Quote of the month

“Our goal is to advance future precision medicine in every clinical setting by enabling clinicians to leverage the power of comprehensive genomic information,”

said Mark Stevenson, Executive Vice President at Thermo Fisher Scientific.

“We can envision a time, one day when patients at local hospitals will have faster access to comprehensive test results that can guide more effective, targeted therapy selection and improved health outcomes.”

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* Specimen-to-report workflow will be available after the Ion Torrent™ Genexus™ Purification System and integrated reporting capabilities are added in 2020. Fully integrated specimen-to-report workflow will be available after the Ion Torrent™ Genexus™ Software 6.4 update.

New Genexus System data

This month, we're excited to share with you consolidated data from our collaborators and early adopters in Europe:

Michael Hummel

Germany

Head of Molecular Pathology Department, University Hospital Charité Institute of Pathology, Berlin

Philip Jermann

Switzerland

Head of Molecular Assay Development Unit Institute of Medical Genetics and Pathology University Hospital, Basel

Nicola Normanno

Italy

Director, Cell Biology and Biotherapy Unit INT-Fondazione Pascale, Naples

Tabetha Sundin

Virginia

Molecular Diagnostics Scientific Director Sentara Healthcare, Norfolk

Jose Luis Costa

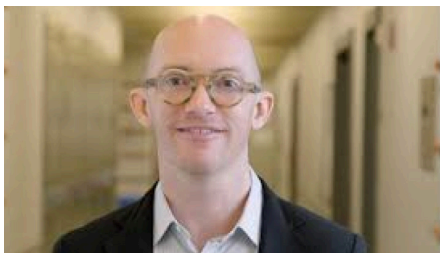
Portugal

Institute of Molecular Pathology and Immunology of the University of Porto

Robert Sebra

New York

Associate Professor of Department of Genetics and Genomic Sciences, Ichan School of Medicine at Mount Sinai, New York



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Data on controls—DNA

Table 1.

Reproducibility table	Basel	Berlin	Naples	IPATIMUP	MSSM	Sentara
True positives	71	74	74	74	73	73
False negatives*	4	1	1	1	2	2
Sensitivity	95%	99%	99%	99%	97%	97%

A custom-developed DNA control with 75 mutations (71 SNVs and 4 INDELs) was tested at six customer sites using the Oncomine Precision Assay and Ion Torrent™ Genexus™ Integrated Sequencer. This control includes mutations in key cancer driver genes such as: *EGFR, ERBB2, KRAS, BRAF, PIK3CA,* and others. **The average sensitivity across six sites was 98%.***

* False negative results were generally due to a low-quality score, which resulted in a NOCALL.

Table 2.

Reproducibility table	Basel	Berlin	Naples	IPATIMUP	MSSM	Sentara
Basel		96%	96%	96%	96%	96%
Berlin	96%		100%	100%	99%	99%
Naples	96%	100%		100%	99%	99%
IPATIMUP	96%	100%	100%		99%	99%
MSSM	96%	99%	99%	99%		99%
Sentara	96%	99%	99%	99%	99%	

The same custom-developed DNA control was tested at six customer sites using the Oncomine Precision Assay and Genexus Integrated Sequencer. This control includes mutations in key cancer driver genes such as: *EGFR, ERBB2, KRAS, BRAF, PIK3CA,* and others. **The overall reproducibility across six sites was 98%.**

Table 3.

	CNV ratio	
Site	*ERBB2*	*FGFR3*
Basel	2.87	2.92
Berlin*	2.66	2.87
Naples	2.76	2.45
Ipatimup	3.22	2.68
MSSM	2.95	3.05
Sensitivity	95%	99%

* Not called due to high MAPD, but CNV ratio included for comparison.

The SeraCare Breast™ CNV Mix control (+3 copies) includes 2 amplified genes (*ERBB2* and *FGFR3*) that are detectable by the Oncomine Precision Assay on the Genexus Integrated Sequencer. **Five (5) customer sites tested the same control and were able to consistently detect the amplified genes with similar CNV ratios.**

Editor's column

The Genexus system was first introduced in November 2019 at the Association for Medical Pathology Annual Meeting & Expo, and to date, already more than 20 instruments have shipped around the world. Six of our collaborator laboratories in Europe and US are, per defined protocol, testing the workflow and performance of the Oncomine Precision Assay. They started with commercial, and one custom made, DNA and RNA controls. The sensitivity, reproducibility, and correlation achieved is between 97–100%, demonstrating very strong overall performance of the Oncomine Precision Assay on the Genexus Integrated Sequencer. These same laboratories are continuing to test their own FFPE and plasma samples. We will bring you those data in the next edition of Genexus News.

Sensitive and reproducible testing of Horizon control with 15 key mutations

The **Horizon Structural Multiplex Reference Standard (HD789)** includes 15 key cancer driver mutations that are detectable by the **Oncomine Precision Assay on the Genexus Integrated Sequencer.** Six customer sites tested the same control with highly sensitive and reproducible results.

Table 4.

Reproducibility table	Basel	Berlin	Naples	IPATIMUP	MSSM	Sentara
True positives	15	15	15	15	15	15
False negatives	0	0	0	0	0	0
Sensitivity	100%	100%	100%	100%	100%	100%

Average sensitivity 100%

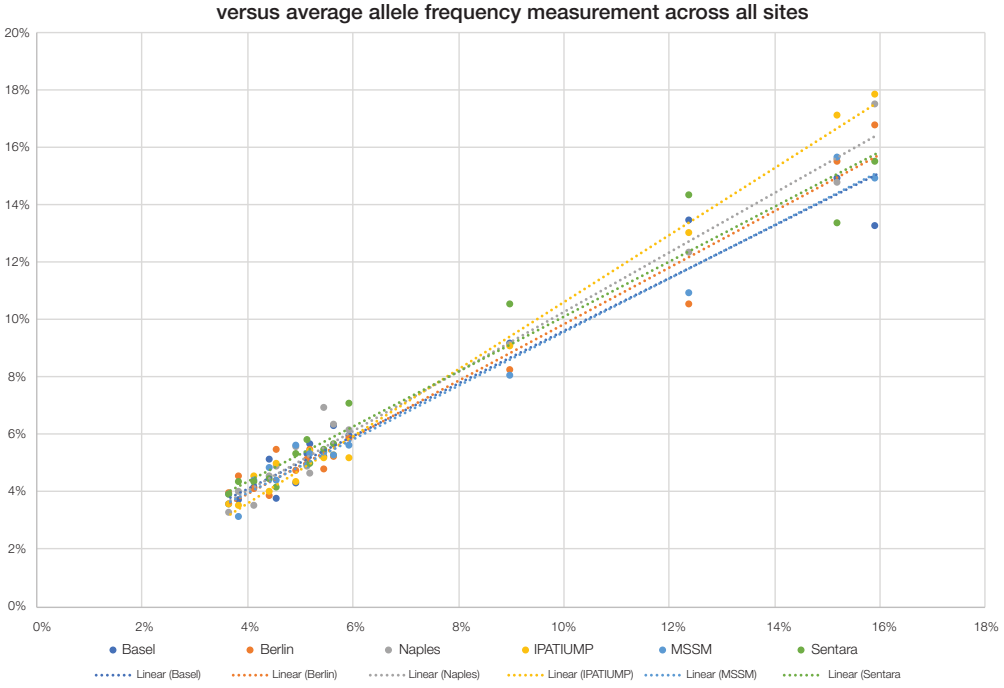
Table 5.

Reproducibility table	Basel	Berlin	Naples	IPATIMUP	MSSM	Sentara
Basel		100%	100%	100%	100%	100%
Berlin	100%		100%	100%	100%	100%
Naples	100%	100%		100%	100%	100%
IPATIMUP	100%	100%	100%		100%	100%
MSSM	100%	100%	100%	100%		100%
Sentara	100%	100%	100%	100%	100%	

Average reproducibility 100%

High correlation of AF measurements using Horizon control across six sites

Figure 1. Allele frequency measurement of 15 hotspot mutations at six customer sites versus average allele frequency measurement across all sites



A correlation coefficient was calculated by comparing the allele frequency of all 15 mutations of the Horizon Structural Multiplex Reference Standard (HD789) as measured by the **Oncomine Precision Assay** and **Genexus Integrated Sequencer** across six customer sites. Results showed a high level of correlation between all sites. The graph compares the AF measurement for each mutation at each site relative to the average AF across all sites for each mutation. **Average correlation was 97%.**

Data on controls—RNA

Table 6.

Expected	Basel	Berlin	Naples	IPATIMUP	MSSM	Sentara
CD74(6) - *ROS1*(34)	●	●	●	●	●	●
EGFR(1) - *EGFR*(8)	●	●	●	●	●	●
EML4(13) - *ALK*(20)	●	●	●	●	●	●
ETV6(5) - *NTRK3*(15)	●	●	●	●	●	●
FGFR3(17) - *BAIAP2L1*(2)	●	●	●	●	●	●
FGFR3(17) - *TACC3*(11)	●	●	●	●	●	●
KIF5B(24) - *RET*(11)	●	●	●	●	●	●
LMNA(2) - *NTRK1*(11)	●	●	●	●	●	●
MET(13) - *MET*(15)	●	●	●	●	●	●
NCOA4(7) - *RET*(12)	●	●	●	●	●	●
SLC34A2(4) - *ROS1*(34)	●	●	●	●	●	●
SLC45A3(1) - *BRAF*(8)	●	●	●	●	●	●
TPM3(7) - *NTRK1*(10)	●	●	●	●	●	●

Average reproducibility 100%

The SeraCare Seraseq™ FFPE Tumor Fusion RNA Reference Material includes 13 unique *ALK*, *ROS1*, *RET*, *NTRK1*, *NTRK3*, *FGFR3*, and *BRAF* fusion isoforms, in addition to *MET*exon14skip. Six (6) customer sites tested the same control that was diluted down to 20% and detected all 13 fusions consistenty. **Therefore the overall reproducibility was 100%.**

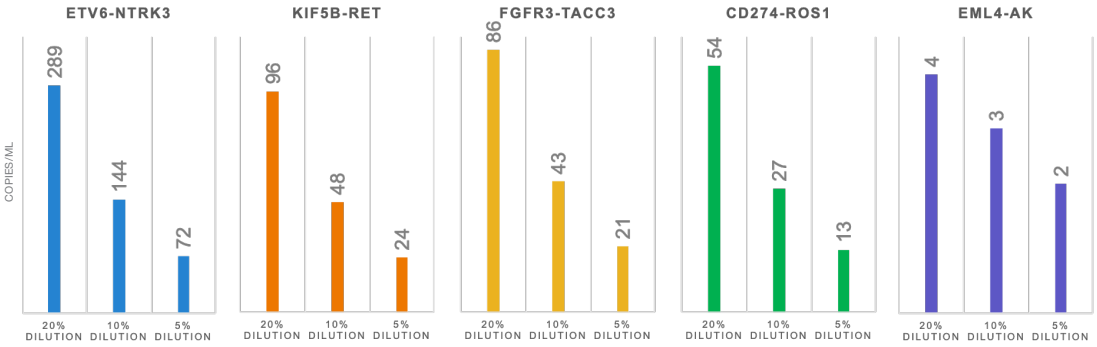
Table 7.

Expected	Basel	Berlin	Naples	IPATIMUP	MSSM	Sentra
AFAP1(14) - *NTRK2*(12)	●	●	●	●	●	●
BTBD1(4) - *NTRK3*(14)	●	●	●	●	●	●
ETV6(4) - *NTRK3*(14)	●	●	●	●	●	●
ETV6(4) - *NTRK3*(15)	●	●	●	●	●	●
ETV6(5) - *NTRK3*(14)	●	●	●	●	●	●
ETV6(5) - *NTRK3*(15)	●	●	●	●	●	●
IRF2BP2(1) - *NTRK1*(10)	●	●	●	●	●	●
LMNA(11) - *NTRK1*(11)	●	●	●	●	●	●
NACC2(4) - *NTRK2*(13)	●	●	●	●	●	●
PAN3(1) - *NTRK2*(17)	●	●	●	●	●	●
QKI(6) - *NTRK2*(16)	●	●	●	●	●	●
SQSTM1(5) - *NTRK1*(10)	●	●	●	●	●	●
TFG(5) - *NTRK1*(10)	●	●	●	●	●	●
TPM3(7) - *NTRK1*(10)	●	●	●	●	●	●
TRIM24(12) - *NTRK2*(15)	●	●	●	●	●	●

Average sensitivity 100% Overall reproducibility 100%

The SeraCare Seraseq™ FFPE N*TRK* Fusion RNA Reference Material includes 15 unique *NTRK* fusion isoforms that are detectable by the **Oncomine Precision Assay on the Genexus Integrated Sequencer.** Six customer sites tested the same control with highly sensitive and reproducible results. Controls were diluted down to 5% in order to reduce the number of copies per fusion.

Figure 2.



4 common fusion isoforms of the SeraCare Seraseq FFPE Tumor Fusion RNA Reference Material v2 were detected by all 6 sites at a 20%, 10%, and 5% dilution of the control, resulting in a range of fusion copies from 289 to 2.

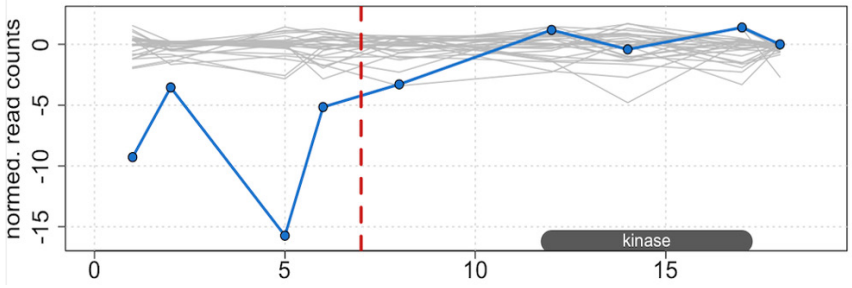
Comparative exon tiling imbalance measurements using RET cell line

A cell line (LC-2/ad) with a known CCDC6-RET fusion was tested using the **Oncomine Precision Assay** and **Genexus Integrated Sequencer** across five customer sites. Across the five sites, all detected the CCDC6-RET fusion with the targeted method. Additionally, all five sites were able to assess the RET fusion using the exon tiling imbalance method as shown below.

Table 8.

Site	Targeted method	Imbalance score (>1.65)	p-value (<0.05)	Passing threshold
Basel	Detected	1.711	0.0019	Both
Naples	Detected	1.725	0.0019	Both
IPATIMUP	Detected	1.753	0.0019	Both
MSSM	Detected	2.251	0.0019	Both
Sentara	Detected	2.097	0.0019	Both

Figure 3.



Representative exon tiling imbalance graph (Basel)

- Blue line indicates expression level across RET
- The relative expression level between the 3’ end (right side) versus the 5’ end (left side) shows a significant imbalance (score of 1.711).
- Also the distinction between the blue and grey lines (fusion baseline) indicates a significant difference (p-value of 0.0019)
- The predicted breakpoint - - - - indicates that the RET fusion includes the full kinase domain; suggesting an activating fusion

Genexus System in other news

LabCorp to adopt the Genexus NGS system and pan-cancer assay

LabCorp announced it will adopt the Genexus System and Oncomine Precision Assay for use in research and development of companion diagnostics as well as other future oncology and precision medicine applications. LabCorp will also evaluate the potential for future deployment of the system and test across its network of laboratories and partner facilities...

Jan 16th, 2020, *LABline*

Ion Torrent Oncomine Myeloid Research Assay reduces turnaround time to 1 day

The Ion Torrent™ Oncomine™ Myeloid Research Assay, the first fully-integrated NGS platform, will be available in 2020 on the new Ion Torrent Genexus System for research use. The platform features automated workflow to allow for result delivery within a single day, requiring minimal user intervention and tissue sample input.

The NGS platform was introduced in November 2019 at the Association for Molecular Pathology Annual and was later demonstrated at the 2019 American Society of Hematology (ASH) Annual Meeting and Exposition. The NGS-based platform will both simplify and accelerate the genomic profiling process, which ordinarily can be time-consuming and laborious for clinical researchers.

Danielle Ternyila, January 7, 2020, *Targeted Oncology*

Simplifying NGS

Based on familiarity with older versions of NGS technology, some providers still perceive NGS as a complex, hard to implement method that requires many samples to be analysed in parallel to be cost efficient. NGS also has a reputation for requiring substantial investments in terms of both instrumentation and highly skilled personnel for sample handling and data analysis. We designed the new Genexus System to simplify NGS and address these challenges in the future.

Anna MacDonald, Jan 06, 2020, *Technology Networks*

Learn more about the Genexus system and Oncomine Precision Assay at **oncomine.com/genexus-oncology** and **thermofisher.com/newday**

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