

IBM Watson Health Oncology and Genomics



Watson for Genomics

VII Simpósio Internacional de Câncer de Pulmão
Março 2019



IBM Watson Health™

Staying up-to-date with genomic information needs a new approach

3 million

Average number of publications related to cancer ¹

117

FDA approved biomarker-based drugs for cancer ³

600%

Increase in % of US pts w/ cancer in 2018 est. to benefit from genome-targeted therapy from 2006 ⁶

25%

The percent of variants of uncertain significance (VUS) that were reclassified ⁷

9 times

NCCN Guidelines changed for NSCLC in 2017 ²

~50%

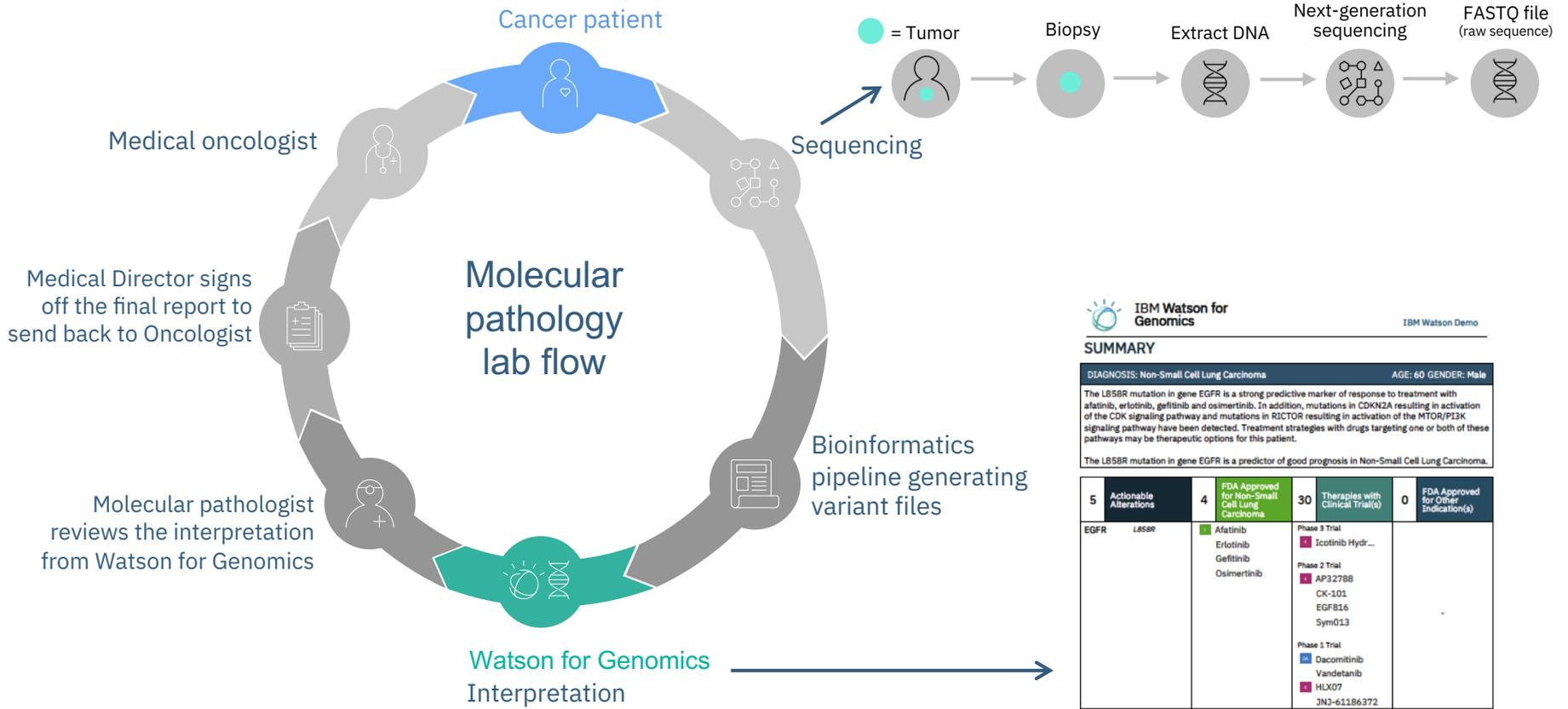
Of new FDA-approved cancer therapies (2016-17) require specific molecular features ⁵

87%

Of Pharma pipe is biomarker driven drugs targeting late-stage cancer ⁴

1. Reyes-Aldasoro CC. The proportion of cancer-related entries in PubMed has increased considerably; is cancer truly “The Emperor of All Maladies”? Novelli G, ed. *PLoS ONE*. 2017;12(3):e0173671. doi:10.1371/journal.pone.0173671.
2. <http://www.lungcancernews.org/2018/06/04/nccn-guidelines-updated-for-2018-keeping-pace-with-data/>, Accessed August 9th, 2018
3. Julianne D. Twomey, Nina N. Brahme, Baolin Zhang, Drug-biomarker co-development in oncology – 20 years and counting, *Drug Resistance Updates*, Volume 30, 2017, Pages 48-62, <https://doi.org/10.1016/j.drug.2017.02.002>.
4. Aitken, M., Kleinrock, M. & Kumar, S. *Global Oncology Trends 2017*. (IQVIA, 2017).
5. Heymach, J. *et al. J. Clin. Oncol.* **36**, 1020–1044 (2018).
6. Marquart J, Chen EY, Prasad V. Estimation of the Percentage of US Patients With Cancer Who Benefit From Genome-Driven Oncology. *JAMA Oncol.* 2018;4(8):1093–1098. doi:10.1001/jamaoncol.2018.1660
7. *JAMA*. 2018;320(12):1266-1274. doi:10.1001/jama.2018.13152

Where does Watson for Genomics fit in a lab workflow



IBM Watson for Genomics
IBM Watson Demo

SUMMARY

DIAGNOSIS: Non-Small Cell Lung Carcinoma **AGE:** 60 **GENDER:** Male

The L858R mutation in gene EGFR is a strong predictive marker of response to treatment with afatinib, erlotinib, gefitinib and osimertinib. In addition, mutations in CDKN2A resulting in activation of the CDK signaling pathway and mutations in RICTOR resulting in activation of the MTOR/P13K signaling pathway have been detected. Treatment strategies with drugs targeting one or both of these pathways may be therapeutic options for this patient.

The L858R mutation in gene EGFR is a predictor of good prognosis in Non-Small Cell Lung Carcinoma.

5	Actionable Alterations	4	FDA Approved for Non-Small Cell Lung Carcinoma	30	Therapies with Clinical Trial(s)	0	FDA Approved for Other Indicator(s)
EGFR	L858R	Afatinib Erlotinib Gefitinib Osimertinib	Phase 3 Trial Icotinib Hydr...	Phase 2 Trial AP32788 CK-101 EGF816 Sym013	Phase 1 Trial Dacomitinib Vandetanib HLX07 JNJ-61186372		

Key features of Watson for Genomics



Comprehensive

Rely on expertly curated, clinical content based on the latest therapeutic options approved including targeted and immunotherapy options, professional guidelines, clinical trial options and relevant publications.



Fast

Save time and help reduce variability across reports with rapid, consistent, efficient and reproducible interpretation across cancer types.



Scalable

Easily scale sample volume and complexity of gene panel – from targeted panels to whole genome.



Evidence-based reporting

Depend on a clearly defined, level-of-evidence model, including pre-clinical information.



SaaS service

Get started easily.
No hardware to purchase.
Minimal configuration required for initial use.



Security & privacy-compliant

Designed to comply with HIPAA and GDPR requirements.

Watson for Genomics system overview



Add Sample

.vcf / .maf, .log2, .dge, .fusion



Watson for Genomics



Report

Add a Sample

Select your files *

You may choose up to 4 files, but can only include 1 of each type: .log2, .fusion, .dge and either .vcf or .maf but not both.

WFG_NSCLC.sample1_ascii.vcf

Browse

Choose a Case ID *

Create a Case ID or choose from an existing case.

NSCLC1

Diagnosis *

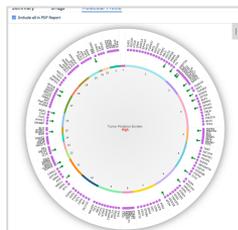
Lung Carcinoma

Optional

Non-Small Cell Lung Carcinoma

* Indicates a required field

Molecular profile analysis



BRCA1 E3490V, E1131S, F1477C/V/D

BRCA1 is a nuclear E3 ubiquitin-protein ligase that specifically mediates the formation of Lys-6-linked polyubiquitously expressed with highest levels in ovaries, testis and thymus. It plays a central role in DNA repair by response to DNA damage. The protein combines with other tumor suppressors, DNA damage sensors, and act a large multi-subunit protein complex known as the BRCA1-associated genome surveillance complex (BASC). It is a component of the RNA polymerase II holoenzyme and functions as a transcriptional coactivator (PubMed: 1115). Germline mutations in BRCA1 predispose with high penetrance to breast and ovarian cancer (PubMed: 79149). Carriers have also an increased risk for pancreatic adenocarcinoma (PubMed: 15761292). In addition, a novel BRCA1 mutation carriers reported an up to 5-fold increased risk for colorectal cancer (PubMed: 24292448). It BRCA1 Z1 grmline mutations account for approximately 25% of inherited breast and ovarian cancers (PubMed: 16836). Associated mutations have been described for this gene. Correlated with its role as a tumor suppressor, it is correlated with the etiology of sporadic breast cancer.

Drug analysis

Summary Drugs Molecular Profile

Include all in PDF Report

- Afatinib, ERBB2, EGFR
- Erlotinib, EGFR
- Gefitinib, EGFR
- Osimertinib, EGFR
- Cobimetinib, MAP2K1 (Phase 2 Trial)
- EGFRi, EGFR (Phase 2 Trial)

Overview Clinical Trials Literature

TOTAL: 2 Refresh Update: 2018-05-20

A Phase 2 Study of EGFRi and Gefitinib in TCR-tumor EGFR-mutant Non-Small Cell Lung Cancer

Conditions: Lung Cancer

Status: Phase 2 Not yet recruiting

Intervention(s): EGFRi, Gefitinib

A Phase II, Open Label, Multi-center Study to Characterize the Safety, Tolerability and Preliminary Efficacy of EGFRi in Combination With Selected Targeted Agent

Conditions: EGFR-mutant Non-small Cell Lung Cancer

Status: Phase 1 Not yet recruiting

Intervention(s): EGFRi, NSCLC1, Tumorid

Summary

High mutation burden, which is a strong predictive marker of response to treatment with immune checkpoint inhibitors, has been detected in this tumor. The E3115* and E3490* missense mutations in MSH2, MSH6 and MMR2, and the E300* mutation and heterozygous copy number loss in gene MSH2 are strong predictive markers of response to treatment with niraparib, olaparib and rucaparib. The E300* mutation and heterozygous copy number loss in gene MSH2 are strong predictive markers of response to treatment with pembrolizumab. In addition, mutations in five genes resulting in activation of the PI3K/AKT/mTOR signaling pathway and mutations in two genes resulting in activation of the RAS/MAPK signaling pathway have been detected. Treatment strategies with drugs targeting one or more of these pathways may be therapeutic options.

Relevance	Alteration	Approved for: Ovarian Neoplasm	Investigational for: Ovarian Neoplasm
	MSH2 Loss E300*	Pembrolizumab	Nivolumab, Atezolizumab, Avelumab, Durvalumab, Nivolumab + Ipilimumab, V93.300004, RECON2010, TIR-082
	MSH6 E3234*	Pembrolizumab	Nivolumab, Atezolizumab, Avelumab, Durvalumab, Nivolumab + Ipilimumab



IBM Watson Demo

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Watson for Genomics reports on actionable mutations, therapeutic options and clinical trials within minutes



IBM Watson for Genomics

IBM Watson Demo

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				Phase 1 Trial Dacomitinib Vandetanib HLX07 JNJ-61186372			

- 1 Automated case summary based on molecular profile
- 2 Automated classification of all genetic alterations
- 3 Clearly defined level of evidence model
- 4 Biomarker based clinical trial association
- 5 Speed and efficiency

- Display variant icons for the following types of mutation:

- Diagnostic mutation: a genetic alteration associated with a specific cancer type
- Cancer predisposing mutation: a genetic alteration associated with increased risk of cancer
- Resistance mutation: a genetic alteration predictive of lack of response to a given therapy
- Prognostic mutation: a genetic alteration predictive of the likely course of the disease
- Germline mutation: a hereditary genetic alteration

Level of evidence

- Each targeted therapy or immunotherapy option match is associated with a level of evidence
- Incorporates drug responsiveness and drug resistance information
- Level of evidence factors into degree of cancer specific clinical relevance of a biomarker in Watson for Genomics

Evidence sources:

- FDA drug labels
- NCCN guidelines
- Case studies
- Clinical and preclinical evidence from the published literature
- Chemotherapy options **not** included

Level of evidence

LEVELS OF EVIDENCE

Level Description

1	1 - Drug is FDA-approved and biomarker is standard of care (SOC) for this indication (excluding chemotherapeutic drugs and hormone therapies)
2A	2A - Drug is FDA-approved and the associated biomarker is predictive of response by NCCN for this indication
2B	2B - Drug is FDA-approved and NCCN recommends the associated biomarker as predictive of response for a different indication. The response in this indication is supported by clinical evidence
3A	3A - Clinical evidence supports the biomarker as being predictive of response to a drug for this indication
3B	3B - Clinical evidence supports the biomarker as being predictive of response to a drug for a different indication
4	4 - Compelling preclinical evidence and/or case study reports support the biomarker as being predictive of response to this drug
R1	R1 - Standard of care biomarker predictive of resistance to an FDA-approved drug for this indication including biomarkers described by the NCCN
R2	R2 - Clinical evidence supports a biomarker not included in NCCN and not standard of care as of being predictive of resistance to an FDA-approved drug

Mutation list format

The screenshot shows a molecular profile interface with two gene entries: BRCA2 and FGFR1. Annotations are overlaid on the page:

- Mutations identified:** Points to the G715* mutation label for BRCA2.
- Variant Level Content:** Points to the detailed variant information for G715*.
- Gene/biomarker:** Points to the 'Amplification, Overexpressed' label for FGFR1.
- Variant Attributes such as log2 ratios, variant allele frequency and read depth can be displayed from input files:** Points to the 'log2=3.0' attribute for the FGFR1 variant.
- Literature citations and link out:** Points to the list of PubMed citations for the FGFR1 variant.
- Gene level content:** Points to the detailed gene description for FGFR1.

Summary **Drugs** **Molecular Profile**

Include all in PDF Report

BRCA2 G715*

BRCA2 is involved in maintenance of genome stability, specifically the homologous recombination pathway for double-strand DNA repair. The protein interacts also with the RAD51 recombinase to regulate homologous recombination. It also targets the recombinase to ssDNA and inhibits ssDNA binding, thereby regulating/enhancing the DNA strand exchange activity of RAD51. In addition, BRCA2 plays a role in mitotic spindle assembly checkpoints through modulation of the level of spindle assembly checkpoint proteins. The expression of BRCA2 is proportional to the rate of cell proliferation. Non-dividing cells do not express the protein, while it is present in actively dividing tissues, including the epithelium of the breast during puberty and pregnancy. A huge number of germline mutations have been identified that are associated with an increased risk of breast cancer in both men and women, as well as several other types of cancer. BRCA2 is a tumor suppressor gene and tumors with BRCA2 mutations generally exhibit loss of the wild-type allele.

G715*
See all notes

More than 2000 BRCA1 and BRCA2 mutations have been identified, the most common ones being small insertion/deletion frameshift mutations, non-synonymous truncations and disruptions of the splice site leading to nonfunctional BRCA proteins (PubMed: 24312913). Inactivating mutations in this and the related BRCA1 gene, if present in the germline, increase the risk for breast and ovarian cancer, and they have been associated with an increased susceptibility to other cancer types as well. BRCA1 and BRCA2 mutations account for about 20 to 25 percent of hereditary breast cancers (PubMed: 11250676) and about 5 to 10 percent of all (sporadic and inherited) breast cancers (PubMed: 18575892). In addition, they are also present in 15 percent of sporadic and inherited ovarian cancers (PubMed: 16284991). Men with BRCA2 mutations are also at increased risk of prostate and breast cancer (PubMed: 18042939, 17213823) and BRCA2 mutation carriers are also at increased risk for the development of pancreatic cancer (PubMed: 19064968). Breast and ovarian cancers associated with BRCA1 and BRCA2 mutations tend to develop at younger ages than their nonhereditary counterparts. The majority of inactivating mutations result in the expression of a truncated protein. Pathogenic germline variants in BRCA2 have been associated with familial breast-ovarian cancer (PubMed: 8524414, 8589730, 9012404, 9145678, 16950820), pancreatic cancer (PubMed: 12097290, 12569143, 25356972, 17301269, 26658419), prostate cancer (PubMed: 18445692, 28067867) and susceptibility to male breast cancer (PubMed: 20587410, 29433453).

FGFR1 Amplification, Overexpressed

FGFR1 is a tyrosine kinase that acts as cell-surface receptor for fibroblast growth factors. The protein plays an essential role in the regulation of embryonic development, cell proliferation, differentiation and migration. FGFR1 signaling is activated by ligand binding resulting in dimerization and autophosphorylation of TK intracellular domains. It then activates the MAPK, necessary for cell cycle progression. FGFR1 dimerization leads to the activation of a number of other signaling molecules including the PI3K/AKT/mTOR pathway, the PLCG pathway, the JAK-STAT pathway, and indirectly, the NFkB pathway. Chromosomal translocations involving FGFR1 and the transforming acidic coiled-coil genes (TACC1 or TACC3) have been described in a subset of GBM. These oncogenic fusion proteins localize to mitotic spindle poles, have constitutive kinase activity and induce mitotic and chromosomal segregation defects (PubMed: 22837387). Focal amplification of FGFR1 occurs with a frequency of up to 20% in squamous cell lung cancer (PubMed: 22960745, 21360078). However, amplification of the gene does not always correlate with increased expression of the protein and not all cell lines and patient-derived tumors with FGFR1 amplification are sensitive to targeted inhibition (PubMed: 24771645, 23082000, 23002168). Further analysis has shown that even similar levels of protein expression do not translate in similar response to treatment and biomarkers to stratify patients have not been identified. Overexpression and/or amplification of FGFR1 has been associated with resistance to endocrine therapy in breast cancer (PubMed: 20179196).

Amplification
log2=3.0
See all notes

FGFR1 is one of the most commonly amplified genes across a variety of cancer types (PubMed: 23658459, 25677745, 21140078). Aberrant activation of the FGFR pathway, including amplification and overexpression of FGFR1, promotes tumorigenesis by mediating cell survival, motility and angiogenesis (PubMed: 15863030, 15863033). Additionally, inhibition of FGFR signaling in the context of amplification has been shown to reduce cell proliferation and promote cell death (PubMed: 17121884, 24265351), suggesting that FGFR1 amplification can be a driving oncogenic alteration. FGFR1 amplification is frequently detected in Invasive Ductal Breast Carcinomas and in clinically advanced/metastatic pure mucinous carcinoma, while rare in non-invasive breast tumors supporting the role of FGFR1 amplification as a marker of aggressive disease (PubMed: 22863309, 26762307). In addition, high FGFR1 expression correlates with high tumor grade, large tumor size. FGFR1 overexpression has been associated with poor relapse-free survival in ER-positive/ERBB2-negative primary breast cancer (univariate, HR: 2.63; p= 0.0019) and it is a predictor of poor outcome in luminal A breast cancers (DFS: log-rank = 8.939, p = 0.003; OS: log-rank = 4.211, p = 0.040) (PubMed: 26801869, 26673008).

Overexpressed
See all notes

The gain of FGFR1 expression is expected to be likely pathogenic. FGFR1 amplification is frequently detected in Invasive Ductal Breast Carcinomas and in clinically advanced/metastatic pure mucinous carcinoma, while rare in non-invasive breast tumors supporting the role of FGFR1 amplification as a marker of aggressive disease (PubMed: 22863309, 26762307). In addition, high FGFR1 expression correlates with high tumor grade, large tumor size. FGFR1 overexpression has been associated with poor relapse-free survival in ER-positive/ERBB2-negative primary breast cancer (univariate, HR: 2.63; p= 0.0019) and it is a predictor of poor outcome in luminal A breast cancers (DFS: log-rank = 8.939, p = 0.003; OS: log-rank = 4.211, p = 0.040) (PubMed: 26801869, 26673008).

LEGEND: ● Predisposing ● Prognosis

Circular plot format

- Global view of all the mutations in the sample
- Organized by chromosome
- Indication of the functional impact of the mutation (e.g, overexpression)
- TMB (if high) also represented within the circular plot
- Interactive: clicking on a gene directs you to its detailed information in the table

Summary

Drugs

Molecular Profile

Include all in PDF Report



Clinical Trial Association

Watson for Genomics matches the patient's molecular profile to available clinical trials with:

- Targeted therapies
- Immunotherapies



Patient information:
age, gender (if
provided),
ER/PR/HER2 (if
breast cancer)

Cancer type

Genetic profile

Drug list

Clinical trial details (sourced from clinicaltrials.gov)

Overview	Clinical Trials	Literature
TOTAL: 7 Refresh Update: 2018-04-17		
Targeted Agent and Profiling Utilization Registry (TAPUR) Study NCT02693535		
Conditions: Solid Neoplasm	Status: Phase 2 Recruiting	Interventions: Pertuzumab, Sunitinib, Vismodegib, Erlotinib, Trastuzumab, Dasatinib, Axitinib, Olaparib, Cetuximab, Read More...
A Phase 2 Study of Olaparib Monotherapy in Metastatic Breast Cancer Patients With Germline or Somatic Mutations in DNA Repair Genes (Olaparib Expanded) NCT03344965		
Conditions: Malignant Breast Neoplasm	Status: Phase 2 Recruiting	Interventions: Olaparib

Export and download of Watson for Genomics reports

- Via User interface and via API

PDF download

- Direct PDF version of report can be downloaded.

JSON download

- Allows download of json reports that can be parsed for content customization or integration with client internal systems.
- Downloads an additional 'filtered variants' excel file to help clients analyze and troubleshoot if required.

IBM Watson for Genomics
Version 38.155



REPORT FOR: IBM Clinical Adoption
ANALYZED ON: May 29 07:07:45 CDT 2018
CASE: Olaner 133
AGE: 38
GENES: Female

SUMMARY

13 Actionable Alterations | **4 FDA Approved for Cancer** | **48 Variants with ClinVar Data** | **3 FDA Approved for COPD**

13 Actionable Alterations with Therapies

Gene	Source	Annotation	Filtered Code	Filtered Reason	
1	GENE	Source	Annotation	Filtered Code	Filtered Reason
2	CDK6	0-450481519	[F_E_007]	log2 value didn't pass the clinical thresholds (2.000 - 0.415 2.000).	
3	MET	-0.07400058	[F_E_007]	log2 value didn't pass the clinical thresholds (2.000 - 0.415 2.000).	
4	FGFR1	-0.40545145	[F_E_007]	log2 value didn't pass the clinical thresholds (2.000 - 0.415 2.000).	
5	MTOR	11.11182209 Gnull_MM_004958	[F_M_002]	Mutation is filtered out because variant type is not in scope.	
6	JAK1	11.65112286 C null_MM_002227	[F_M_002]	Mutation is filtered out because variant type is not in scope.	
7	MYCN	12.16984127 Gnull_MM_005378	[F_M_002]	Mutation is filtered out because variant type is not in scope.	
8	ALK	12.29879703 C null_MM_004304	[F_M_002]	Mutation is filtered out because variant type is not in scope.	
9	IDH1	12.209113174 A11A:NM_005896	[F_M_002]	Mutation is filtered out because variant type is not in scope.	
10	PDGFR4	14.55121552 G null_MM_006206	[F_M_002]	Mutation is filtered out because variant type is not in scope.	
11	ALK	12.29816366 G[C]	[F_M_002]	Mutation is benign. It is found 14.5% in EAS population from GENOMAD database.	
12	PDGFR4	14.55133718 G.192:IGV:NM_00621	[F_M_004]	Inactivating LOF is in conflict with GDF role of PDGFR4 in cancer.	
13	REF	110.43617913 V9577:NM_020975	[F_M_004]	Inactivating LOF is in conflict with GDF role of REF in cancer.	
14	FGFR4	15.179517197 C[T]	[F_M_002]	Mutation is benign. It is found 98.9% in EAS population from GENOMAD database.	
15	GNAX1	19.80409379 C.6735A:NM_020272	[F_M_004]	Inactivating LOF is in conflict with GDF role of GNAX1 in cancer.	
16	ALK	12.29816572 T[C]	[F_M_002]	Mutation is benign. It is found 100.0% in EAS population from GENOMAD database.	
17	ATK1	18.15026585 W22:NM_01014411	[F_M_004]	Inactivating LOF is in conflict with GDF role of ATK1 in cancer.	
18	CDK6	loss-of-function	[F_G_003]	Functional impact for the gene conflicts with GDF role of CDK6 in cancer.	
19	MYCN		[F_G_005]	None of the alterations in MYCN is in scope.	
20	CNDS1		[F_G_005]	None of the alterations in CNDS1 is in scope.	
21	TMB	TMB count: 11 muts. TMB normalized: [F_T_002]		TMB didn't exceed the threshold.	

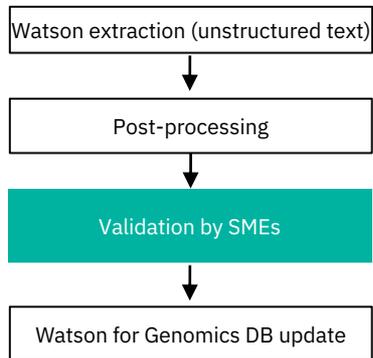


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Artificial intelligence used to amplify the curation process



Literature Refresh

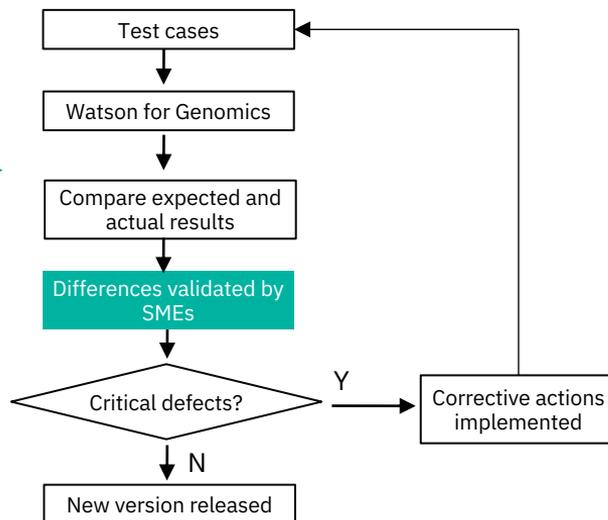


Automated step

Manual step



Expert Validation



Watson for Genomics
interpretation

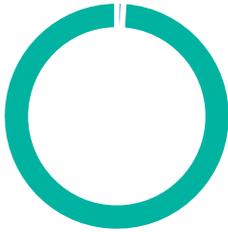
The Oncologist 2017;22:1–7, Supplemental Materials

The Oncologist: Watson for Genomics found 99% of the actionable mutations identified by the molecular tumor board

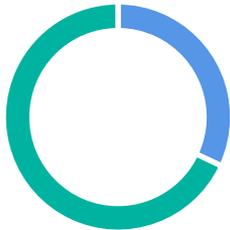
Patel N, et al. *The Oncologist*. 2018;23(2):179-185.



< 3 min



99%



32%

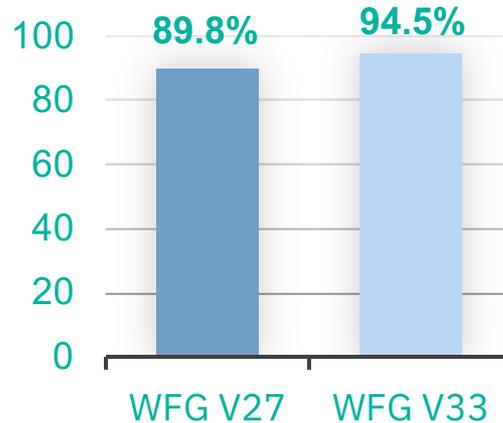
Watson for Genomics took less than 3 minutes per case. Found 99% of the actionable mutations identified by UNC’s MTB and identified additional actionable mutations that the MTB did not in 32% of the cases (N = 1,018)

“Molecular tumor boards empowered by cognitive computing can significantly improve patient care by providing a fast, cost-effective, and comprehensive approach for data analysis in the delivery of precision medicine.” -The Oncologist

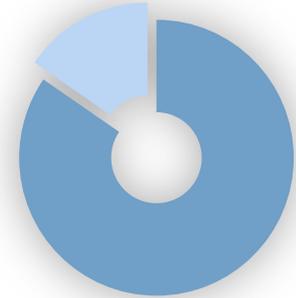
**excerpt from manuscript*

Frontiers in Medicine: Evaluating clinical genome sequence analysis by Watson for Genomics

Itahashi, et al. *Frontiers in Medicine*. 5:305. doi:10.3389/fmed.2018.00305, 2018



Concordance between WfG and expert panel for mutation pathogenicity (N = 198); 12 months between versions



84.6%
Concordance between WfG and expert panel for targeted therapies (N = 198)

“WfG [Watson for Genomics] may be useful in cases where large amounts of genomic data is available, such as whole exon sequences, and in institutions with an insufficient number of experts in gene analyses.”

*excerpt from manuscript

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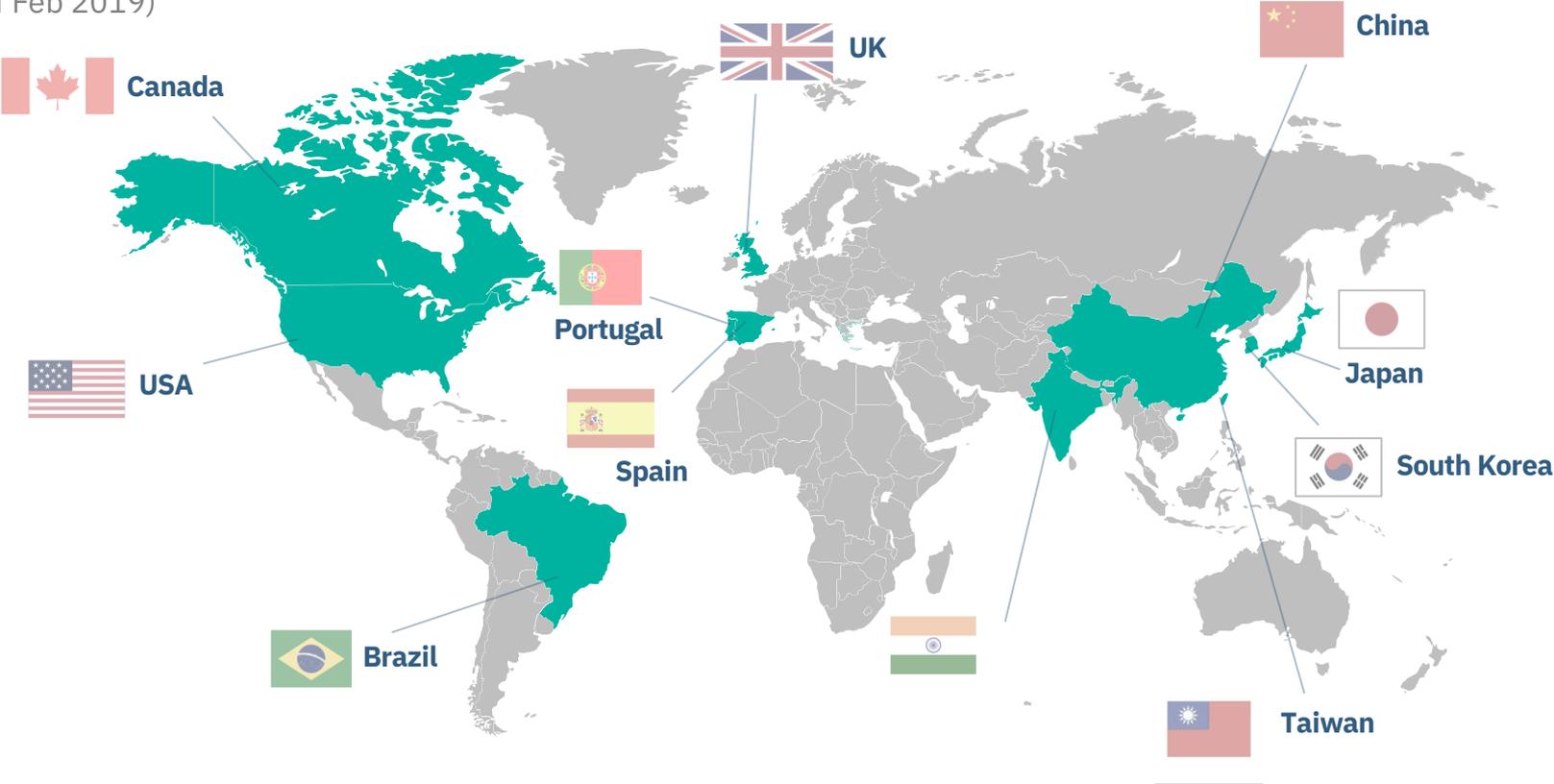
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Appendix

Watson for Genomics : Worldwide implementations

(as of Feb 2019)



Our vision

Leverage AI to provide expertly validated, up-to-date, comprehensive content to enable clinical reporting

Value:

- Expertly curated, variant information and clinical content based on the latest therapeutic options, professional guidelines, clinical trial options and relevant publications.
- Clearly defined level-of-evidence model, including clinical and pre-clinical information.
- Rapid, efficient, and reproducible interpretation across cancer types
- Easily scale sample volume and complexity of gene panels
 - from targeted panels to whole genome.



Watson for Genomics ingests diverse inputs

Application	Information type	Supported format
Substitutions and short indels	SNVS and indels	.vcf or .maf *
Copy number change	Copy number variants	.log2 or .vcf
Gene rearrangements	Fusions/ translocations	.fusion or .vcf
mRNA differential expression	Gene expression data	.dge
Immuno-oncology biomarkers	Tumor Mutation Burden & Microsatellite Instability	TMB: .vcf or TMB value/status MSI: Status (High, Low, Stable)

- Uploaded files for each case can contain either a .vcf or .maf but not both
- Watson for Genomics supports GRCh37/ hg19