Integrated report using the Ion Reporter and Oncomine™ Reporter

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Pathologie-DNA

PATHOLOGIE DNA
Efficiënte topdiagnostiek

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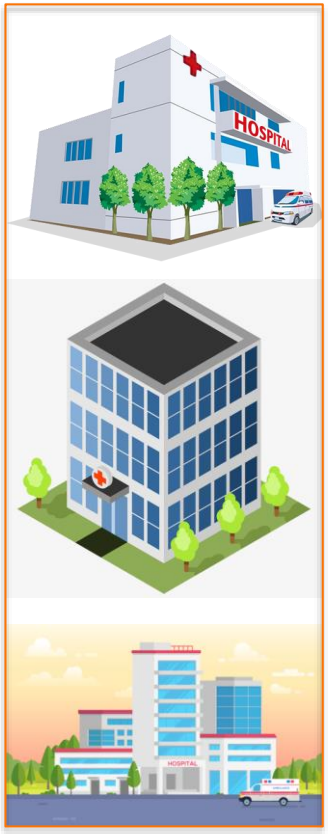
Outline

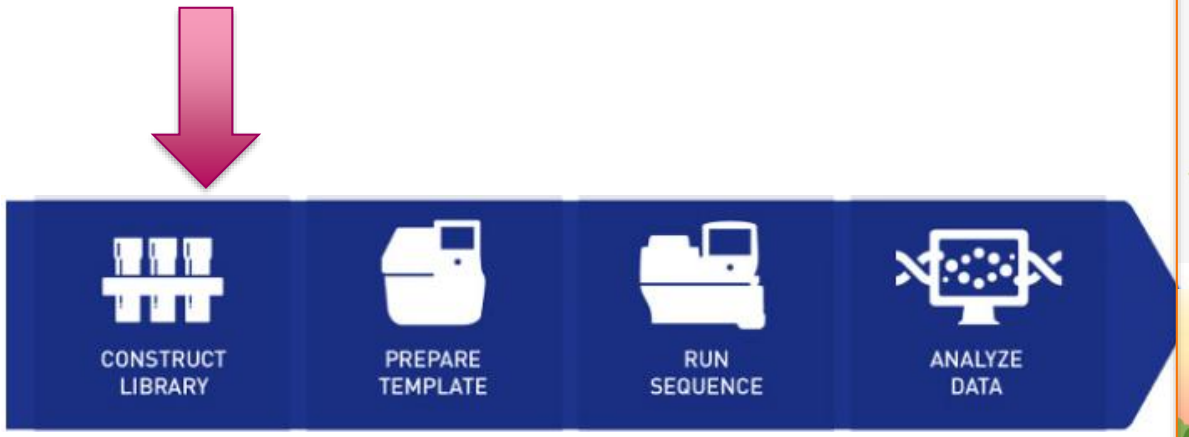
- Pathologie-DNA
- Mutation detection in centralized NGS-facility
- PGM vs. S5 workflow
- Oncomine Reporter
- Preliminary results/Cases
- Conclusions

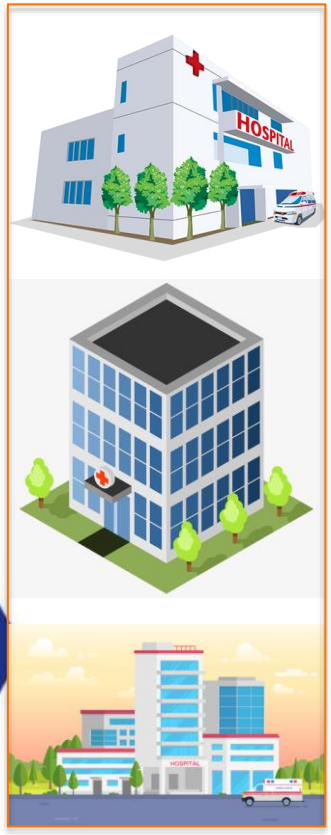
Pathologie-DNA

Mutation detection in centralized NGS-facility



- Order
- Tissue cutting etc.
- Transport to centralized Pathologie-DNA NGS facility, loc. AZN





- Reporting to local LIMS using ICT

Ion PGM™ vs Ion GeneStudio™ S5 Prime

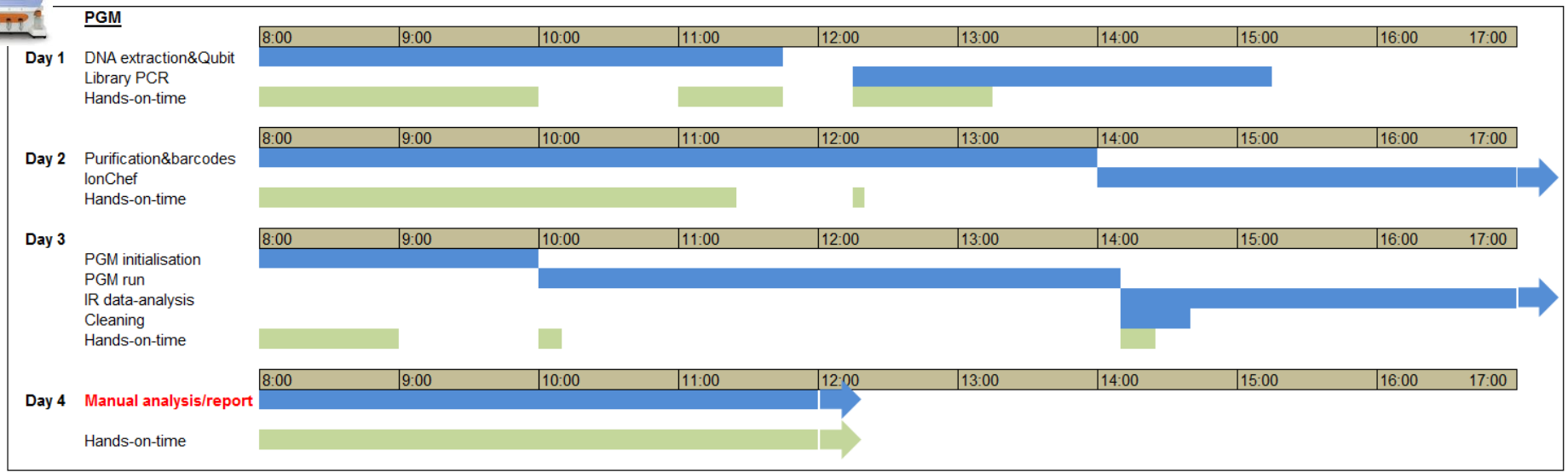
Dependent on Chip:
- 0,4M-5,5M reads
- 0,1-2 Gigabases

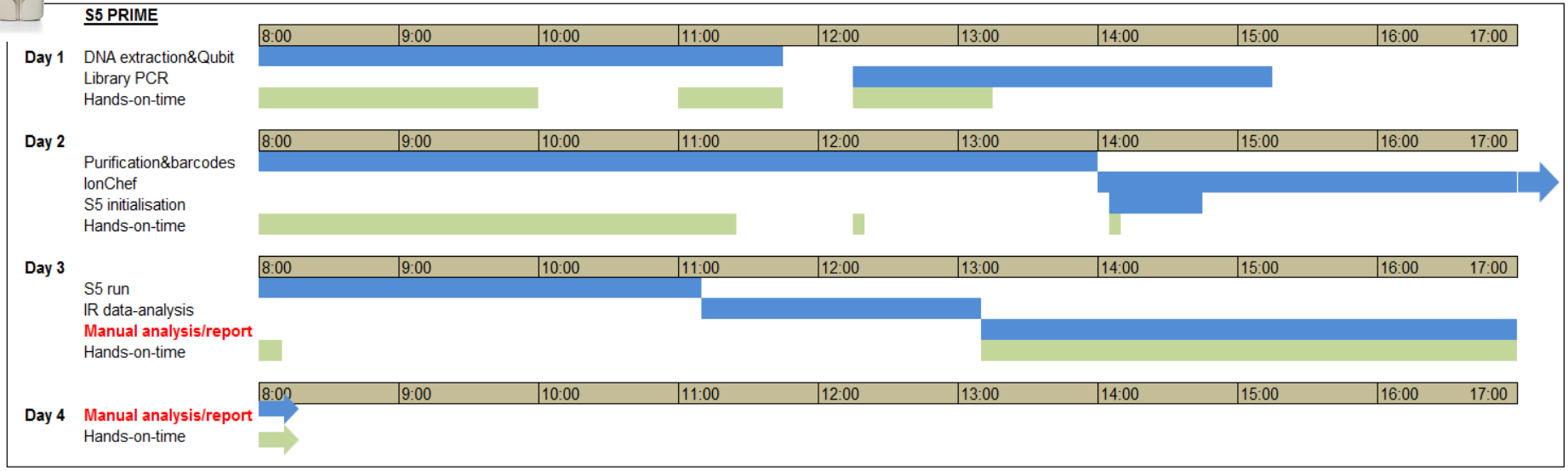
Panels:
- OST (22 genes)
- CHPv2 (50 genes)
- RNA fusion (3 genes)

Dependent on Chip:
- 2M-130M reads
- 0,3-50 Gigabases

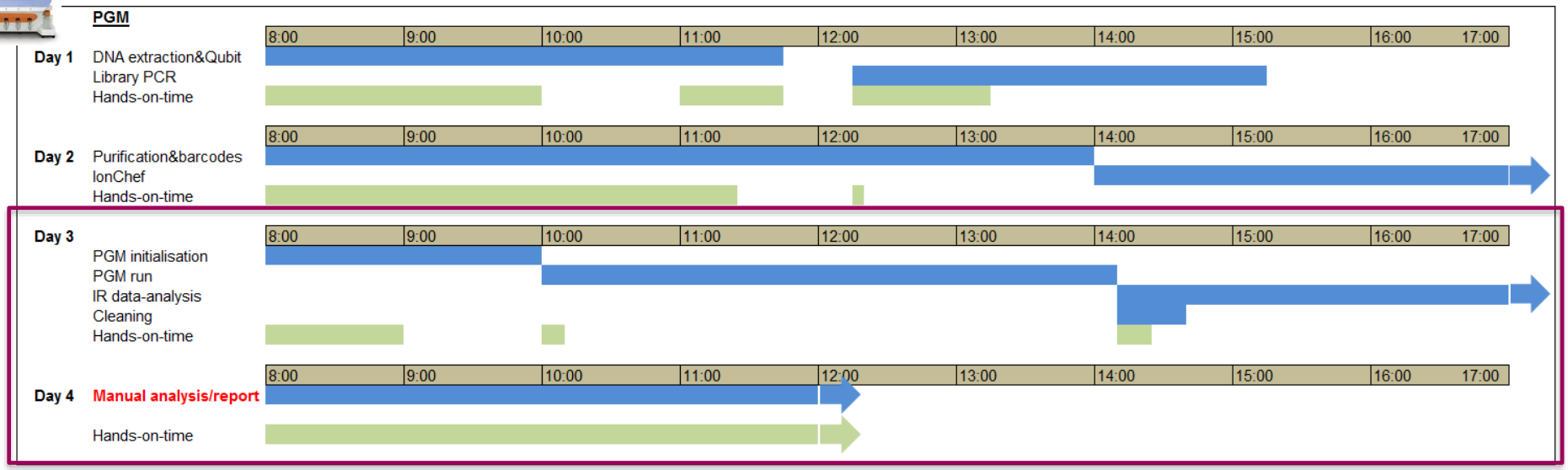
Panels:
- OST panel (22 genes)
- CHPv2 panel (50 genes)
- RNA fusion (3 genes)
- Focus (35 genes, 19 CNV, 23 fusion genes)
- Comprehensive (86 genes, 48 full length genes, 47 CNV, 51 fusion genes)
- Tumor mutational burden (409 genes)
- Liquid biopsy cfDNA Lung (11 genes)

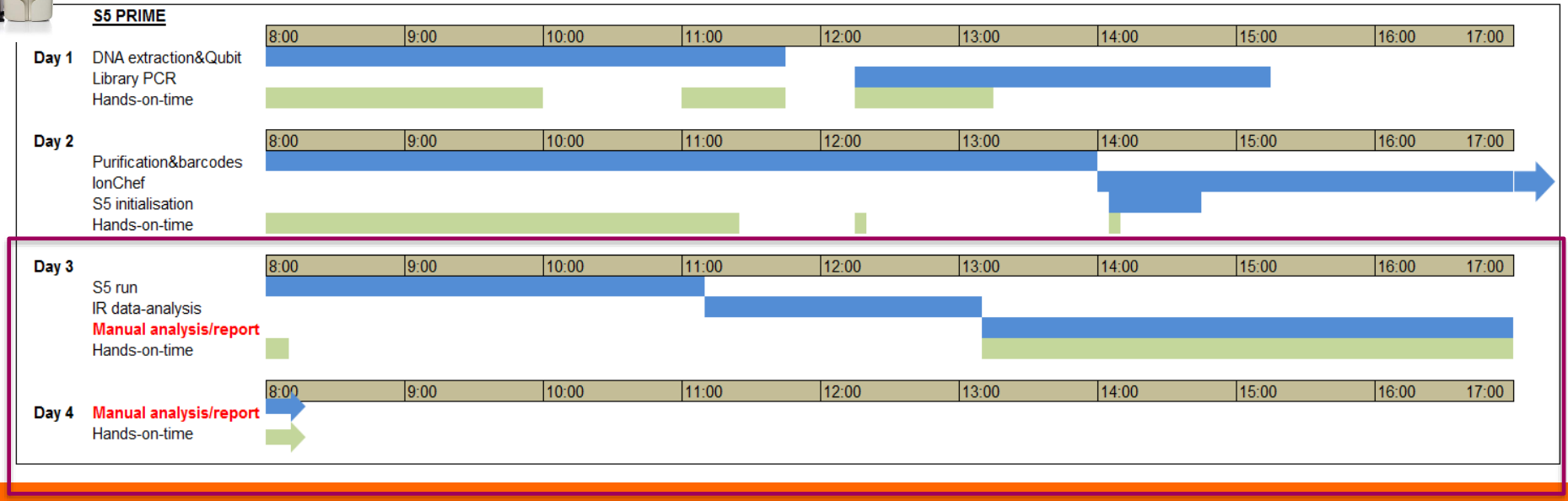
PGM vs S5 PRIME: OST workflow





PGM vs S5 PRIME: OST workflow





PGM vs S5 PRIME

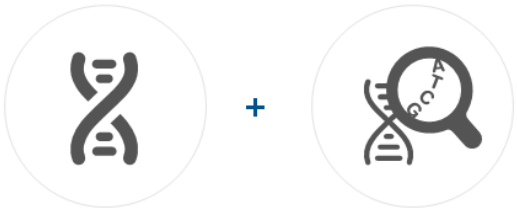
- Impact of S5 PRIME vs PGM
  - Reduction of hands-on time (~1.5 hours)
  - Reduction of time-to-result (≥0.5 day)
  - Increased ease of use (cartridge-based RFID tagged reagents)
  - Increased sequencing capacity; higher number of samples and more complex panels (influences time-to-result)

Oncomine™ Reporter

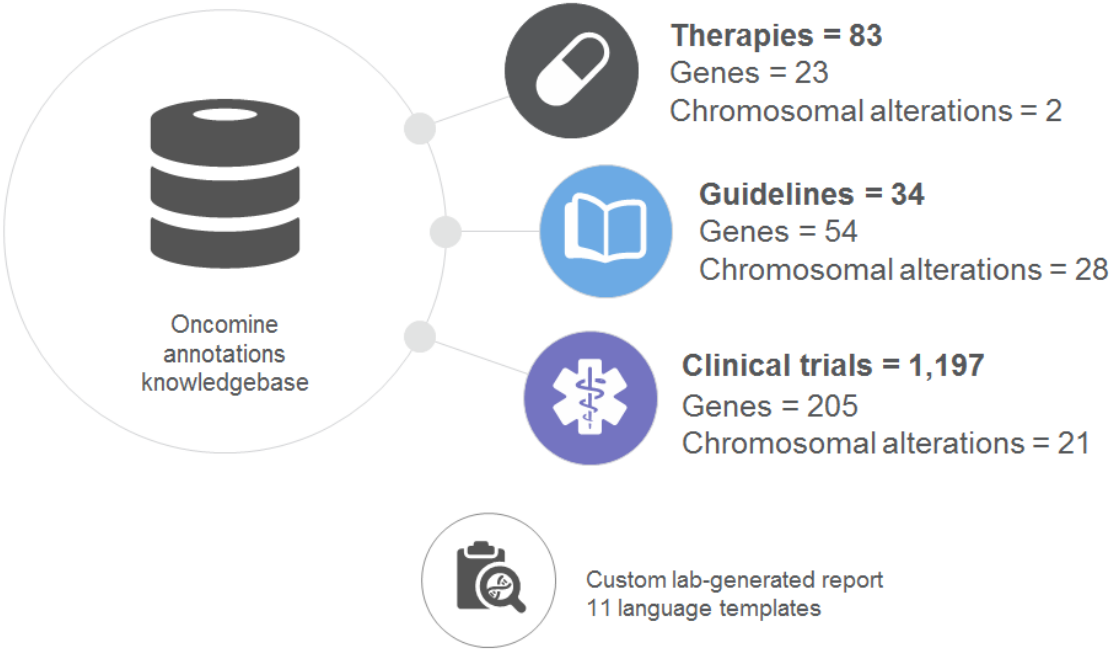
- Increased sequencing capacity/more complex panels
  - Need for systematic mutation calling and classification
  - Preference for software package that does interpretation
    - Standardized
    - Up-to-date
    - Easy to use

- Oncomine™ Reporter: selection of 11 cases
  - Combination of different (hotspot) mutations
  - Non-hotspot mutations (e.g. non-V600 BRAF)

Oncomine™ Reporter Content & Curation



- **42** cancer types, plus two additional categories: unknown primary origin and other cancer type
- **4** sources for labels and guidelines
- **68** countries with enrolling trials



Slide courtesy of Thermo Fischer Scientific

Oncomine™ Reporter Content & Curation

Content

Two key forms of relevant content across 42 cancer types

Clinical consensus*

- Clinical consensus information provided for research is reflected from published, approved therapies, and current treatment guidelines based on genetic event status
- Collected from US and European sources: FDA, NCCN™, ESMO, EMA

Global clinical trials

- Global clinical trials with open enrollment in which genetic events are used as enrollment criteria
- Collected from public and private data sources, including **clinicaltrials.gov**

Curation

Two-reviewer process

- Each piece of candidate evidence is manually curated and standardized by multiple independent reviewers for context, categorization, and concordance
- The process helps ensure that the data are comparable where there are differing reporting standards from global sources
- A team of data managers, cancer biologists, systems engineers, and biostatisticians carefully guide the data through this meticulous data collection and curation workflow

* **Clinical consensus:**
For Ion Torrent™ Oncomine™ Reporter, clinical consensus content is defined as information on published and approved therapies, and current treatment guidelines based on genetic event status put forth by a governmental or other medical, clinical, or physician-accepted authority, such as the FDA, NCCN™, ESMO, and EMA.

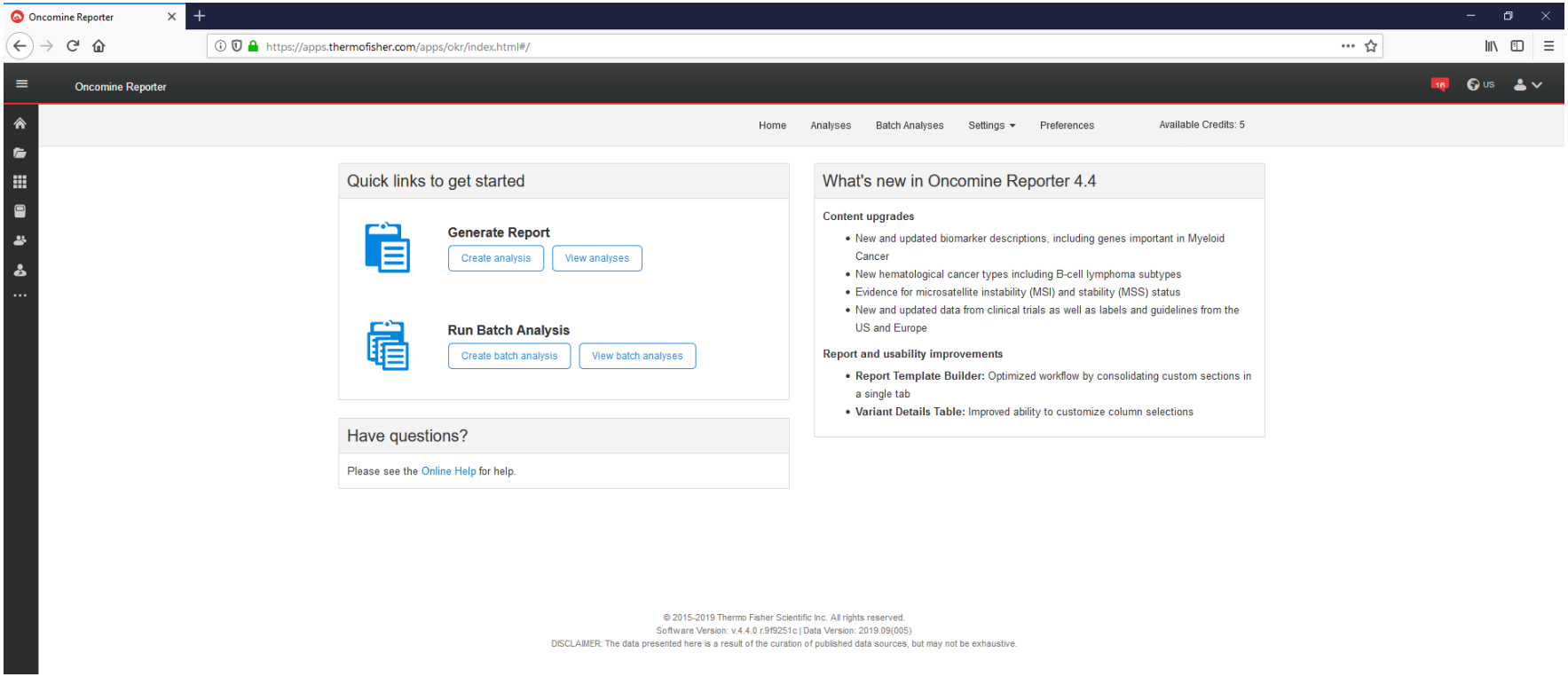
- **Quality content:** Meticulously curated data, updated quarterly

Slide courtesy of Thermo Fischer Scientific

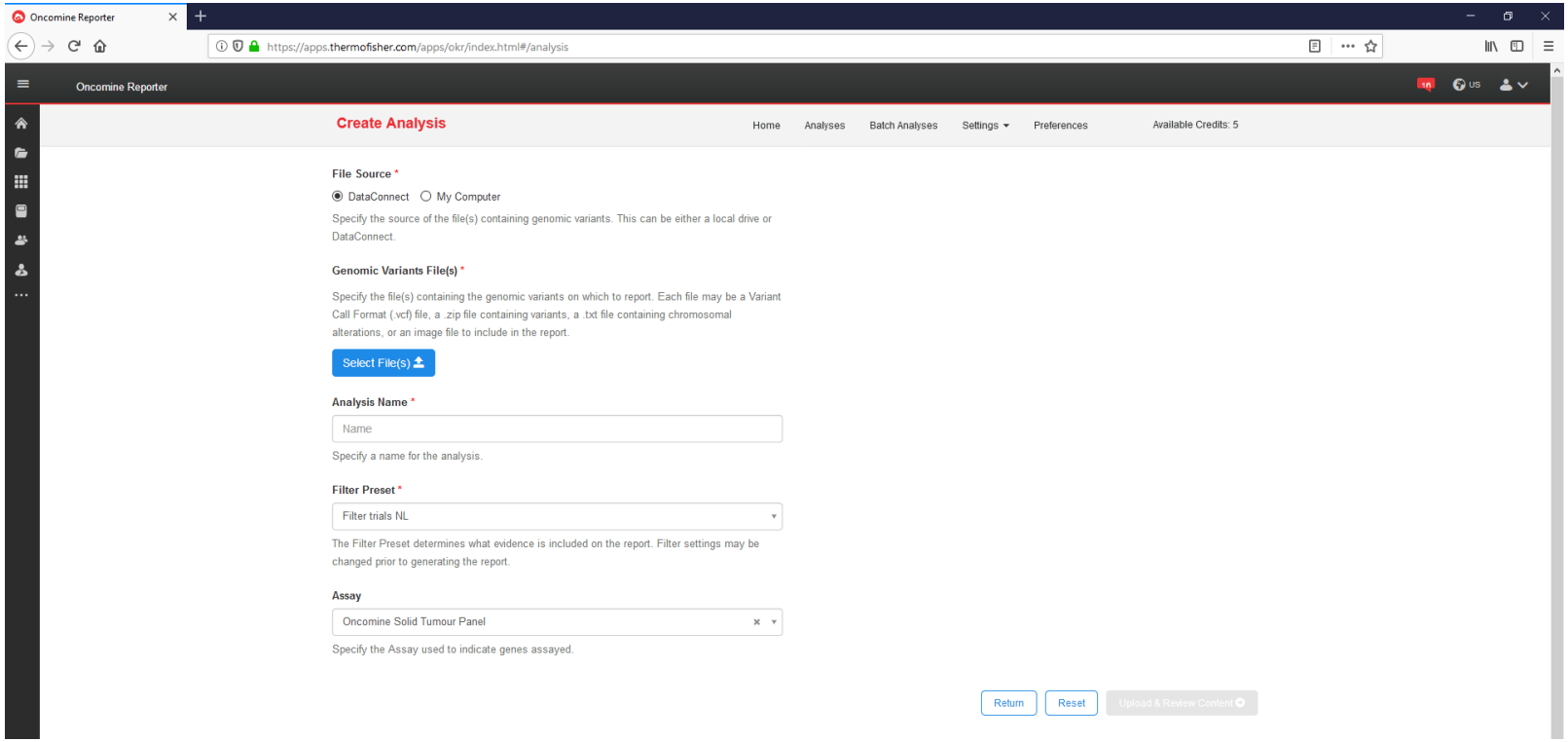
Oncomine™ Reporter: workflow

- Uses Ion Reporter VCF files
- Upload on website ThermoFisher
- Create new case
- Analyse
- Generate report

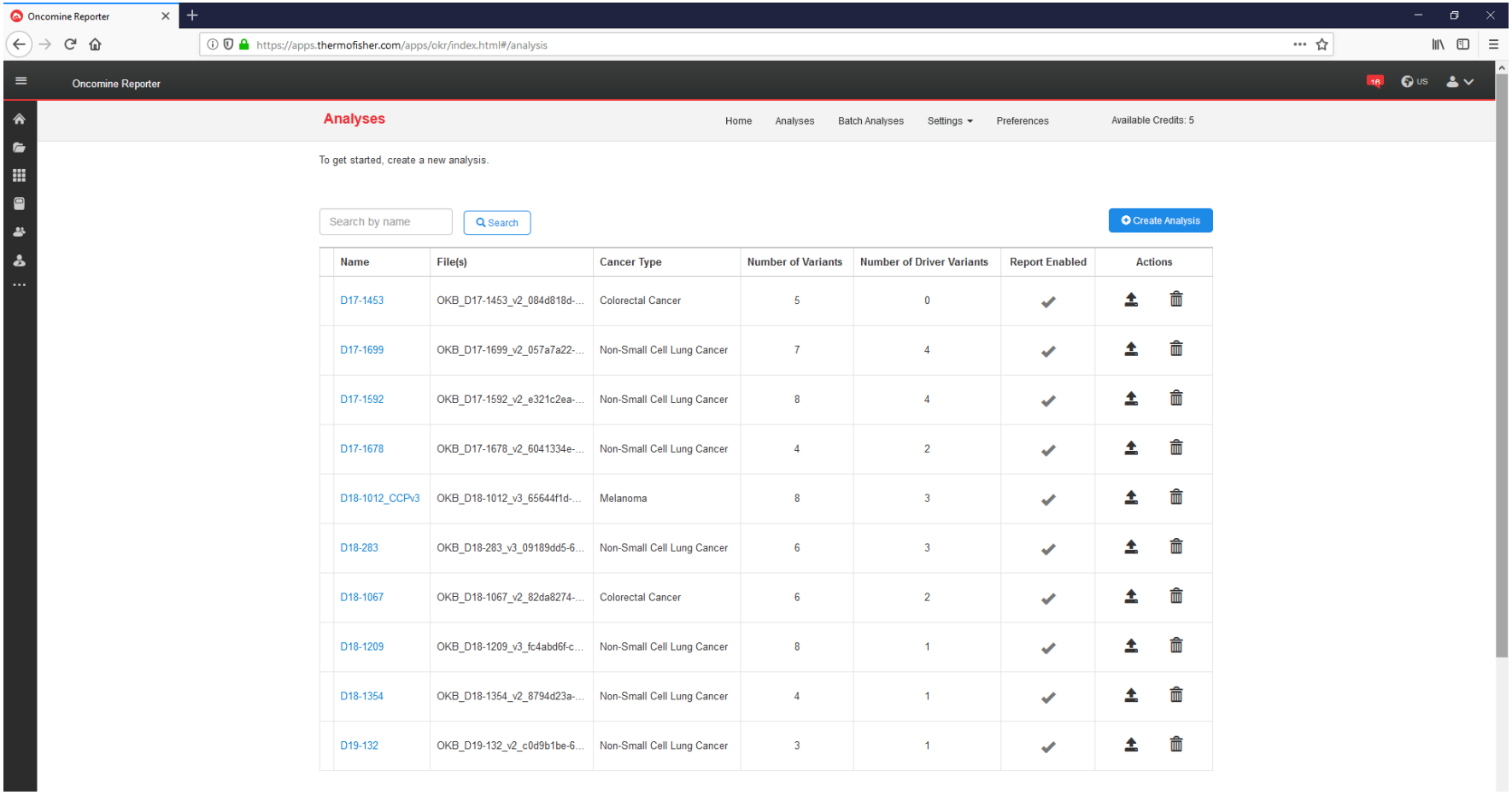
Oncomine™ Reporter: home screen



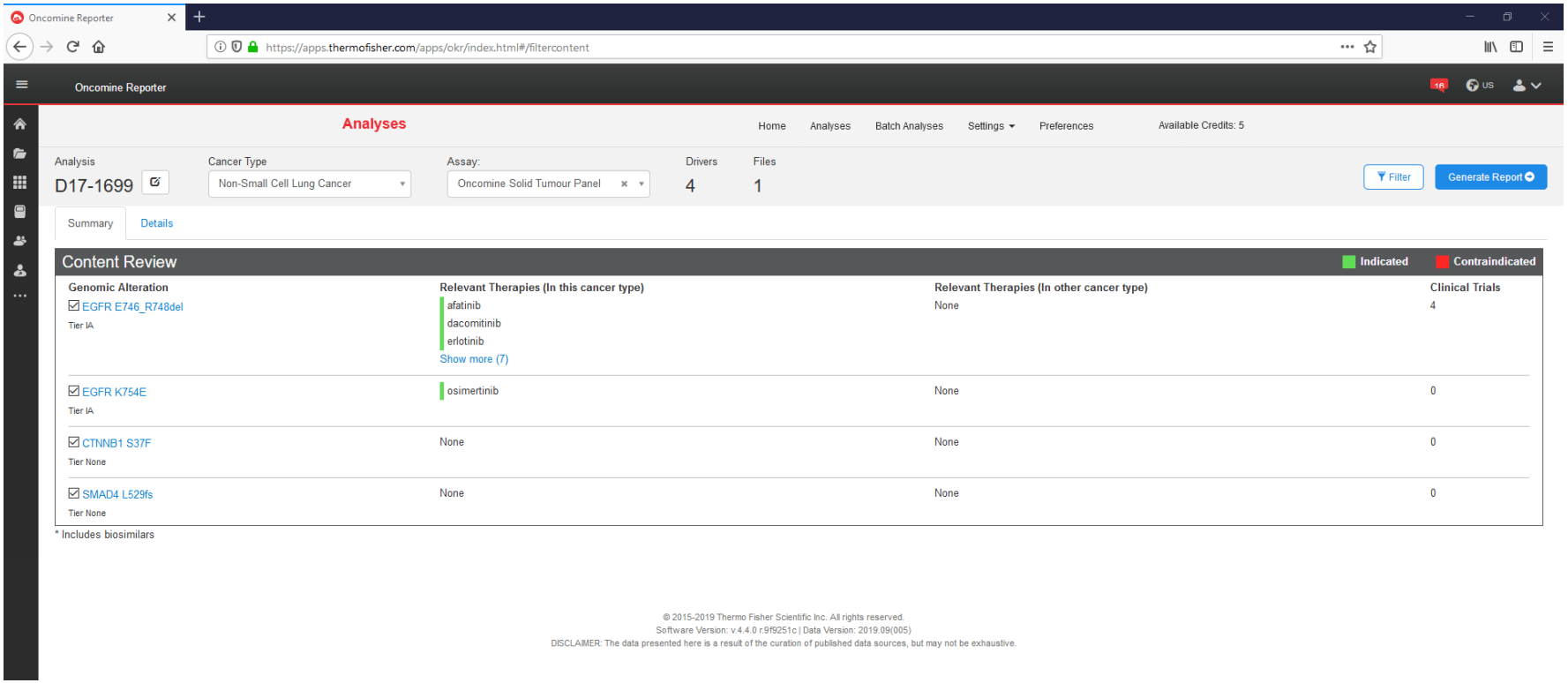
Oncomine™ Reporter: create new case



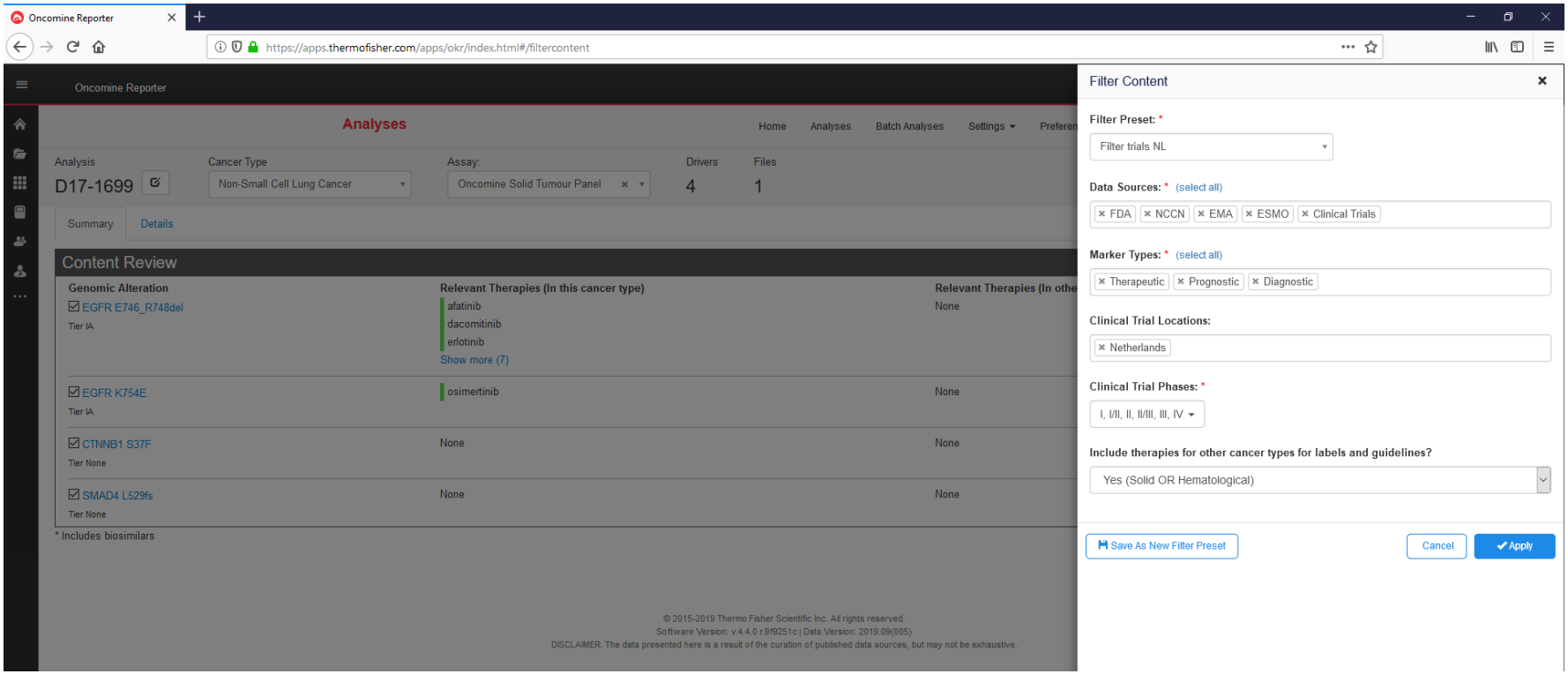
Oncomine™ Reporter: analyses overview



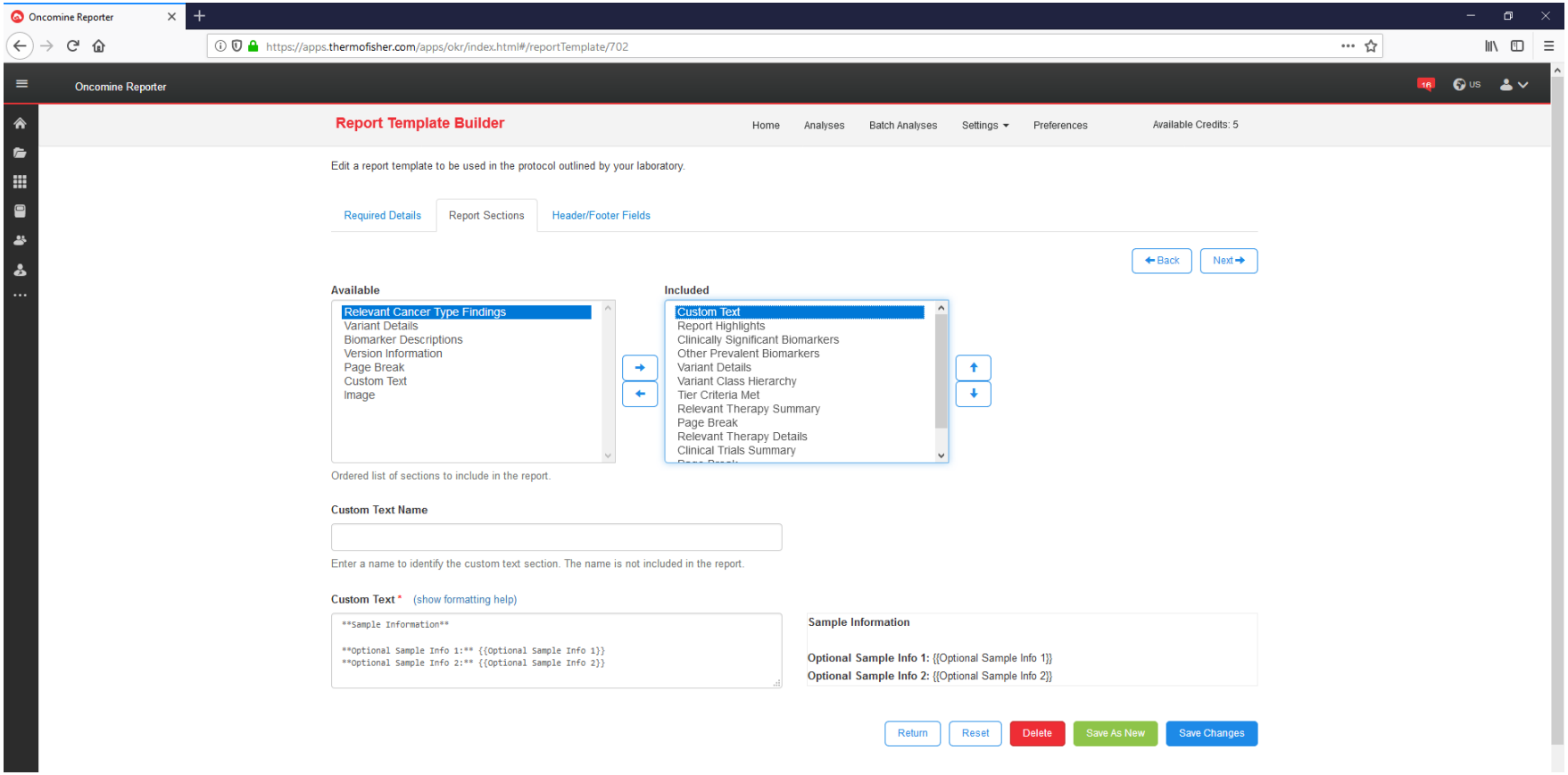
Oncomine™ Reporter: sample overview



Oncomine™ Reporter: filter settings



Oncomine™ Reporter: report settings



Example of Oncomine™ Reporter: Case 1

Sample Information

Optional Sample Info 1: Tnr
Optional Sample Info 2: D17-1592

Sample Cancer Type: Non-Small Cell Lung Cancer

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Report Highlights

3 Clinically Significant Biomarkers
11 Therapies Available
3 Clinical Trials

Example of Oncomine™ Reporter: Case 1

Clinically Significant Biomarkers

Indicated ■ Contraindicated

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
EGFR p.(L861Q) c.2582T>A epidermal growth factor receptor Tier: IA Allele Frequency: 91.46%	afatinib [1, 2] dacomitinib erlotinib gefitinib [2] osimertinib afatinib + cetuximab gefitinib + chemotherapy bevacizumab + erlotinib bevacizumab + gefitinib atezolizumab + bevacizumab + chemotherapy	None	3
EGFR p.(S768I) c.2303G>T epidermal growth factor receptor Tier: IA Allele Frequency: 90.66%	afatinib [1] dacomitinib erlotinib gefitinib [2] osimertinib afatinib + cetuximab gefitinib + chemotherapy bevacizumab + erlotinib bevacizumab + gefitinib atezolizumab + bevacizumab + chemotherapy	None	2
PIK3CA p.(H1047R) c.3140A>G phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha Tier: IIC Allele Frequency: 30.62%	None	alpelisib + fulvestrant [1]	0

Example of Oncomine™ Reporter: Case 1

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
PIK3CA	p.(H1047R)	c.3140A>G	COSM775	chr3:178952085	30.62%	NM_006218.2	missense
EGFR	p.(S768I)	c.2303G>T	COSM6241	chr7:55249005	90.66%	NM_005228.3	missense
EGFR	p.(L861Q)	c.2582T>A	COSM6213	chr7:55259524	91.46%	NM_005228.3	missense
TP53	p.(G334A)	c.1001G>C	.	chr17:7574026	88.82%	NM_000546.5	missense
FGFR3	p.(=)	c.1959G>A	.	chr4:1807894	100.00%	NM_001163213.1	synonymous
MET	p.(=)	c.534C>T	.	chr7:116339672	66.16%	NM_001127500.1	synonymous
MET	p.(N375S)	c.1124A>G	COSM710	chr7:116340262	67.28%	NM_001127500.1	missense
TP53	p.(P72R)	c.215C>G	.	chr17:7579472	100.00%	NM_000546.5	missense

Example of Oncomine™ Reporter: Case 1

Tier Criteria Met

Genomic Alteration	Tier Classification for Non-Small Cell Lung Cancer
EGFR p.(L861Q) c.2582T>A Tier: IA	IA: Biomarker predicts response or resistance to FDA or EMA approved therapies in this cancer type IA: Biomarker is included in NCCN or ESMO guidelines that predict response or resistance to therapies in this cancer type IIC: Biomarker is an inclusion criteria for clinical trials
EGFR p.(S768I) c.2303G>T Tier: IA	IA: Biomarker predicts response or resistance to FDA or EMA approved therapies in this cancer type IA: Biomarker is included in NCCN or ESMO guidelines that predict response or resistance to therapies in this cancer type IIC: Biomarker is an inclusion criteria for clinical trials
PIK3CA p.(H1047R) c.3140A>G Tier: IIC	IIC: Biomarker predicts response or resistance to FDA or EMA approved therapies in other cancer types

Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

Example of Oncomine™ Reporter: Case 1

Clinical Trials Summary

EGFR p.(L861Q) c.2582T>A

NCT ID	Title	Phase
No NCT ID	A Randomized Phase III Study Of Erlotinib Compared To Intercalated Erlotinib With Cisplatinum Pemetrexed As First-Line Therapy For Advanced EGFR Mutated Non-Small-Cell Lung Cancer. The NVALT-17 Study	III
NCT03784599	Trastuzumab-emtansine and Osimertinib Combination Treatment to Target HER2 Bypass Track Resistance in EGFR Mutation Positive NSCLC	II
NCT03114319	An Open-label, Multi-center, Phase I, Dose Finding Study of Oral TNO155 in Adult Patients With Advanced Solid Tumors	I

EGFR p.(S768I) c.2303G>T

NCT ID	Title	Phase
NCT03784599	Trastuzumab-emtansine and Osimertinib Combination Treatment to Target HER2 Bypass Track Resistance in EGFR Mutation Positive NSCLC	II
NCT03114319	An Open-label, Multi-center, Phase I, Dose Finding Study of Oral TNO155 in Adult Patients With Advanced Solid Tumors	I

Example of Oncomine™ Reporter: Case 2

Sample Information

Optional Sample Info 1: Tnr
Optional Sample Info 2: D18-1067

Sample Cancer Type: Colorectal Cancer

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Clinical Trials Summary	3

Report Highlights
2 Clinically Significant Biomarkers
1 Therapies Available
5 Clinical Trials

Clinically Significant Biomarkers

Indicated Contraindicated

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
PIK3CA p.(E545K) c.1633G>A phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha Tier: IIC Allele Frequency: 29.16%	None	alpelisib + fulvestrant [1]	0
KRAS p.(G12S) c.34G>A KRAS proto-oncogene, GTPase Tier: IA Allele Frequency: 56.66%	cetuximab [1, 2] panitumumab [1] cetuximab + chemotherapy [2] panitumumab + chemotherapy [2]	None	5

Sources included in relevant therapies: FDA1, NCCN, EMA2, ESMO

Example of Oncomine™ Reporter: Case 2

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
PIK3CA	p.(E545K)	c.1633G>A	COSM125370	chr3:178936091	29.16%	NM_006218.2	missense
KRAS	p.(G12S)	c.34G>A	COSM517	chr12:25398285	56.66%	NM_033360.3	missense
FGFR3	p.(F386L)	c.1156T>C	COSM724	chr4:1806131	57.87%	NM_001163213.1	missense
FGFR3	p.(=)	c.1959G>A	.	chr4:1807894	100.00%	NM_001163213.1	synonymous
EGFR	p.(=)	c.2361G>A	.	chr7:55249063	100.00%	NM_005228.3	synonymous
MET	p.(T1010I)	c.3029C>T	COSM707	chr7:116411990	38.50%	NM_001127500.1	missense

Tier Criteria Met

Genomic Alteration	Tier Classification for Colorectal Cancer
PIK3CA p.(E545K) c.1633G>A Tier: IIC	IIC: Biomarker predicts response or resistance to FDA or EMA approved therapies in other cancer types
KRAS p.(G12S) c.34G>A Tier: IA	IA: Biomarker predicts response or resistance to FDA or EMA approved therapies in this cancer type IA: Biomarker is included in NCCN or ESMO guidelines that predict response or resistance to therapies in this cancer type IIC: Biomarker is included in NCCN or ESMO guidelines that predict response or resistance to therapies in other cancer types IIC: Biomarker is an inclusion criteria for clinical trials

Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

Example of Oncomine™ Reporter: Case 2

Clinical Trials Summary

KRAS p.(G12S) c.34G>A

NCT ID	Title	Phase
NCT02162563	Treatment Strategies in Colorectal Cancer Patients With Initially Unresectable Liver-only Metastases CAIRO5 a Randomized Phase III Study of the Dutch Colorectal Cancer Group (DCCG)	III
NCT02703571	A Phase I/II Study of Safety and Efficacy of Ribociclib (LEE011) in Combination With Trametinib (TMT212) in Patients With Metastatic or Advanced Solid Tumors	I/II
NCT02754141	A Phase I/IIa Study of BMS-986179 Administered Alone and in Combination With Nivolumab (BMS-936558) in Subjects With Advanced Solid Tumors	I/II
NCT03082209	An Open-Label, Phase I, First-In-Human Study of Safety and Tolerability of TRAIL Receptor Agonist ABBV-621 in Subjects With Previously Treated Solid Tumors and Hematologic Malignancies	I
NCT02607813	A Phase I Dose Finding Study of Oral LXH254 in Adult Patients With Advanced Solid Tumors Harboring MAPK Pathway Alterations	I

Conclusions

- Overall impression and benefits
  - Easy to use and navigate through software
  - Analysis is very quick
  - Extensive information on therapeutic options and available trials
  - Possibilities to adapt report to include all the information you need about specific variants

Future directions

- Integration of software in routine diagnostics
  - Some adaptations to current workflow
    - Automated generation of Oncomine Reporter cases from NGS data, instead of manual upload

- Expectations from clinicians
  - Content of report
  - Ease-of-use for clinic
  - Length of report

Acknowledgements

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