Precision Oncology – Standards and challenges for personalized, evidence-based and translational cancer therapy in clinical routine

Damian Rieke
Department of Hematology, Oncology and Cancer Immunology, Campus Benjamin Franklin, Charité – Universitätsmedizin Berlin

Comprehensive Cancer Center, Charité – Universitätsmedizin Berlin

Hasso-Plattner-Institut, 01.12.2022

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1. Background
2. Standards
3. Challenges
4. Summary

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Background

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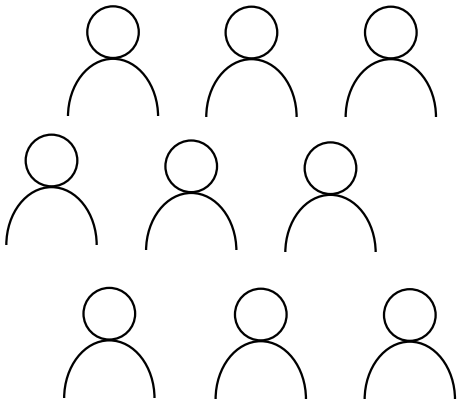

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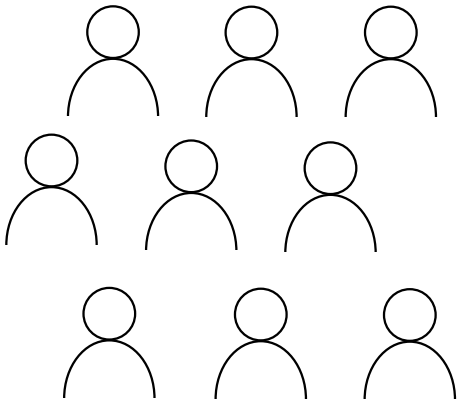
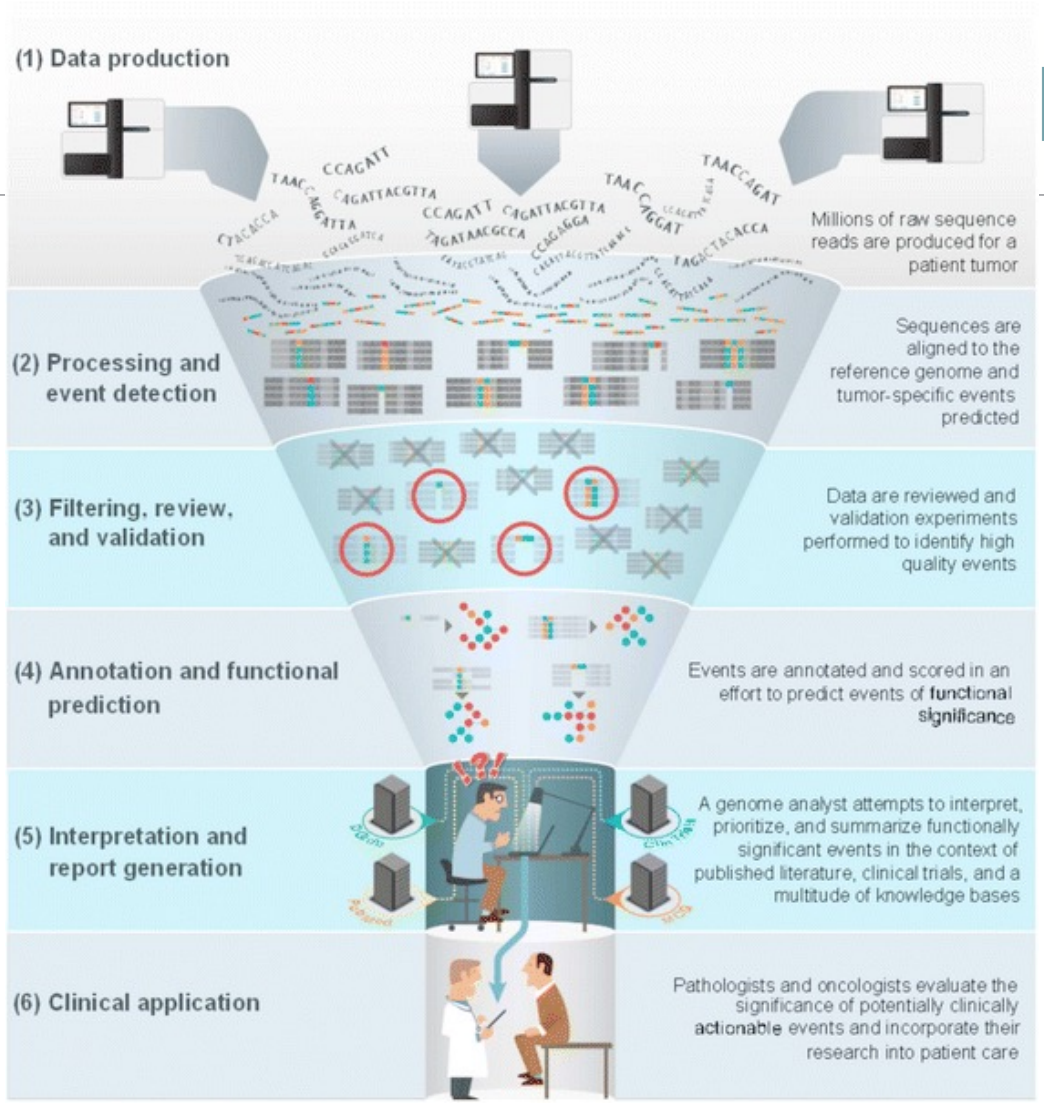


Good et al. Genome Biol . 2014



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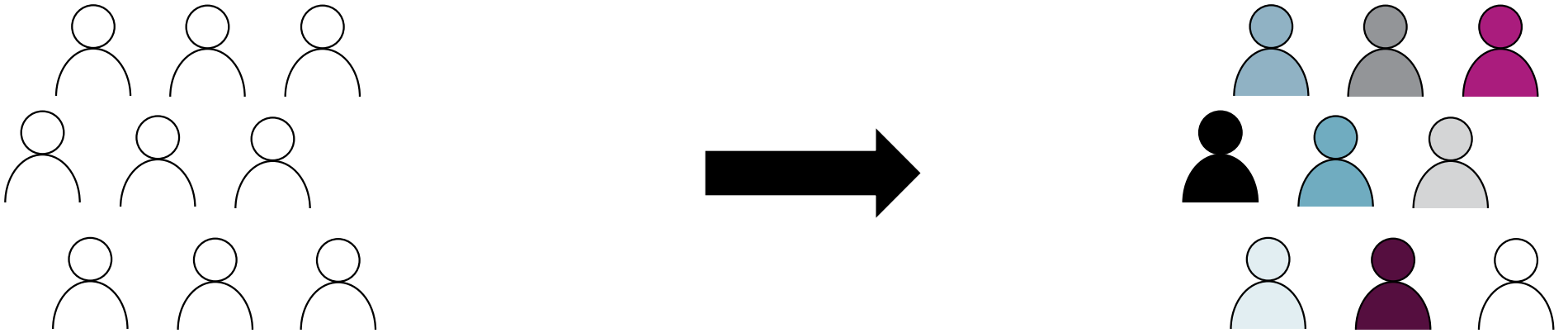

Background

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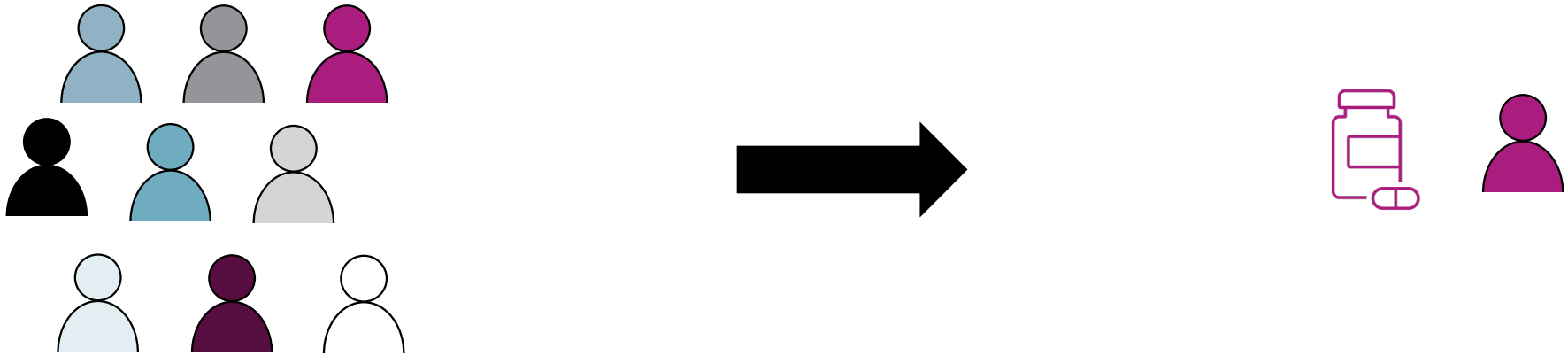

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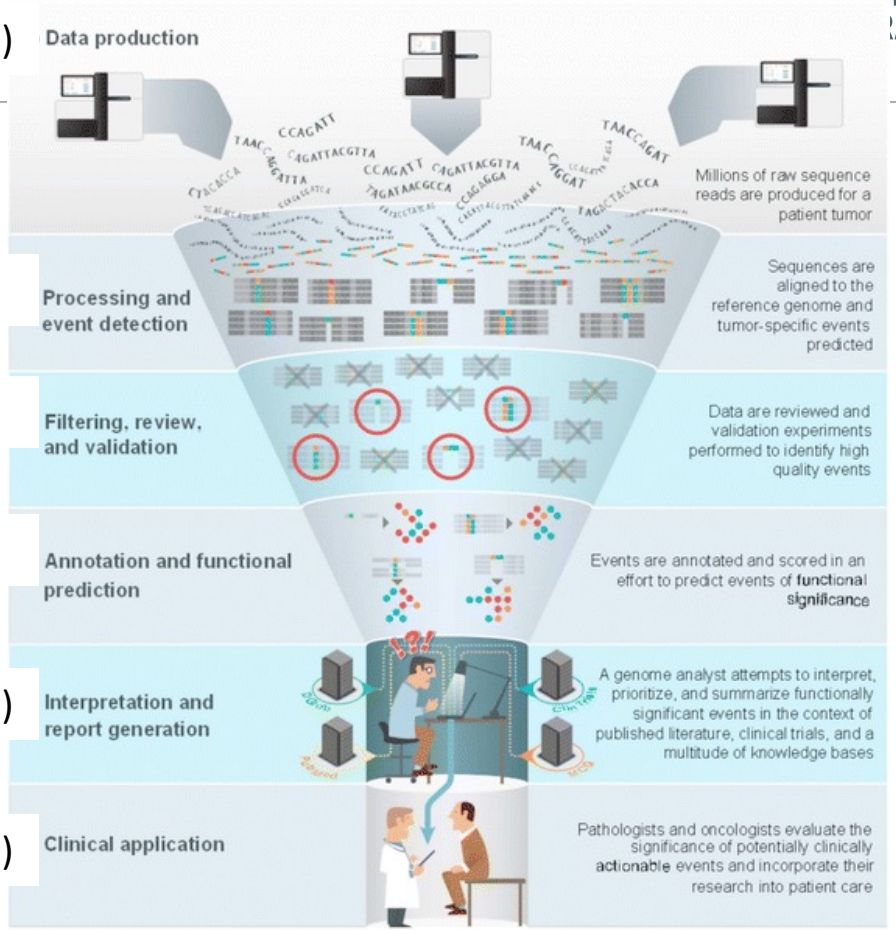
Standards

Good et al. Genome Biol . 2014

(1) Sample selection

(2) Technology selection

(3)



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(6) Follow-up/Trial infrastructure

Standards

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Pat. *1975

Met. Colon Cancer 2020

Good et al. Genome Biol . 2014

Standards

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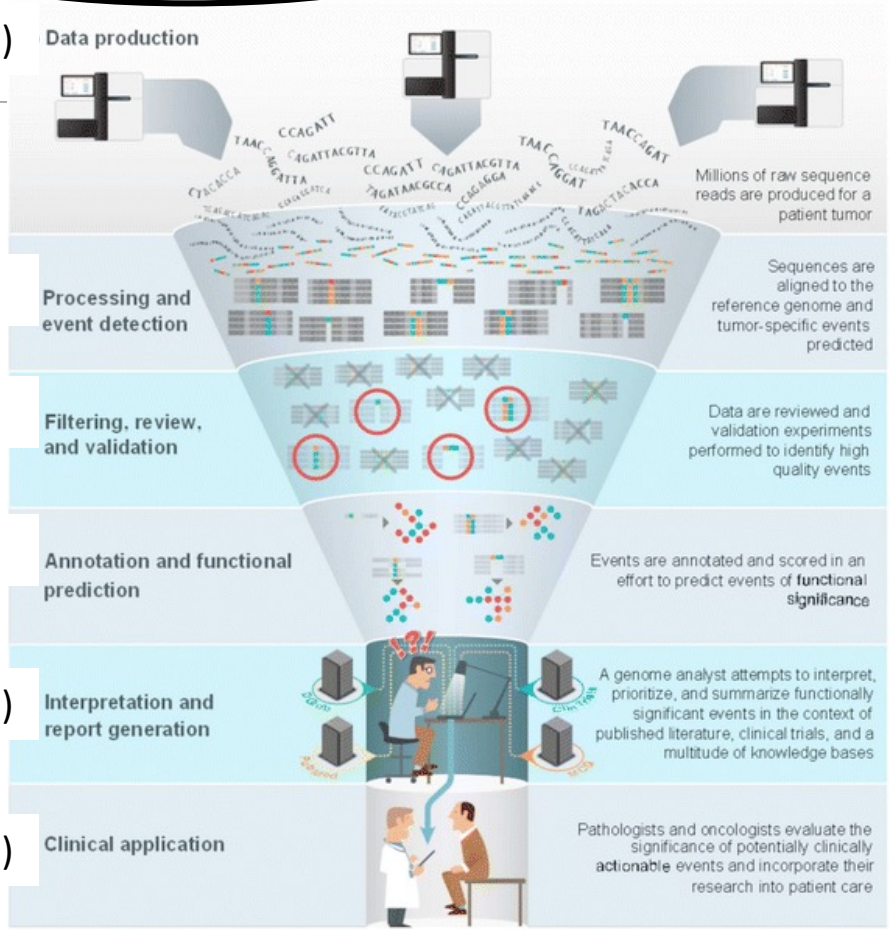

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Präzisionsonkologische Sprechstunde

Für Patientinnen, Patienten & Interessierte

Für Ärztinnen, Ärzte & medizinisches Personal

Für Wissenschaftlerinnen & Wissenschaftler

Forschung

Karriere

Präzisionsonkologische Sprechstunde

Die präzisionsonkologische Sprechstunde am Charité Comprehensive Cancer Center bietet die Möglichkeit einer additiven Diagnostik für Patient:innen der Charité, für Betroffene aus externen Kliniken sowie onkologischen Praxen.

Durchsuchen Sie diese Website

Präzisionsonkologische Sprechstunde - Reevaluation und unabhängige Beratung bei soliden Tumoren

Standards

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Met. Colon Cancer 2021
Molecular Pathology (KRAS-Test): KRAS/NRAS wt
Met. Spread: pulm, hep, local

01/2021	Diagnosis of met. CRC
	Resection
03/21-10/21	FOLFOX/Beva
11/21	pulmonary/hepatic metastases
12/21	14x FOLFIRI/Beva
06/22-09/22	Bevacizumab monotherapy
09/22	Surgery, local tumor progression

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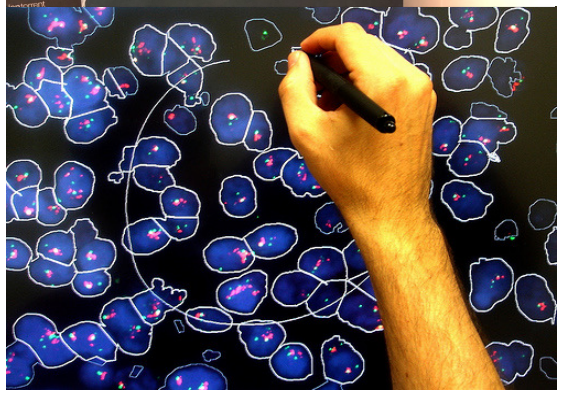
Portfolio
Molecular Diagnostics Pathology, Charité



NGS (accredited/validated)

- Oncomine Focus/Precision DNA Assay
- Oncomine Focus/Precision RNA Assay
- ColonLung Panel V2
- Cancer Hotspot Panel
- Myeloid Panel (Custom)
- (B-cell) Lymphoma Panel
- Oncomine cfDNA (Liquid Biopsies)
- Breast cfDNA Panel (Liquid Biopsies)
- BRCA1/2 Panel
- Tumor Mutational Burden (1.7 Mbases)
- Molecular Health 600+ Panel (3 Mbases); NextSeq
- Oncomine Comprehensive Assay V4 (500+) Panel
- TSO500 (DNA/RNA) Panel
- Ig/TCR Clonality Panel
- Archer RNA Panel

IHC/FISH

- nTRK screening
- TMB
- Other Targets (e.g. HER2, AR…)
- Fusion Gene validation

Other

- e.g. EPIC (Methylom)

DKTK MASTER

- WES/WGS
- RNASeq

ExLiquid

- ctDNA

Functional Analyses

(1) Sample selection
(2) Technology selection

Standards

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Pat. *1975

NGS (accredited/validated)
- **Molecular Health 600+ Panel (3 Mbases); NextSeq**
- **Archer RNA Panel**

IHC/FISH
- **HER2**
- **MMR**

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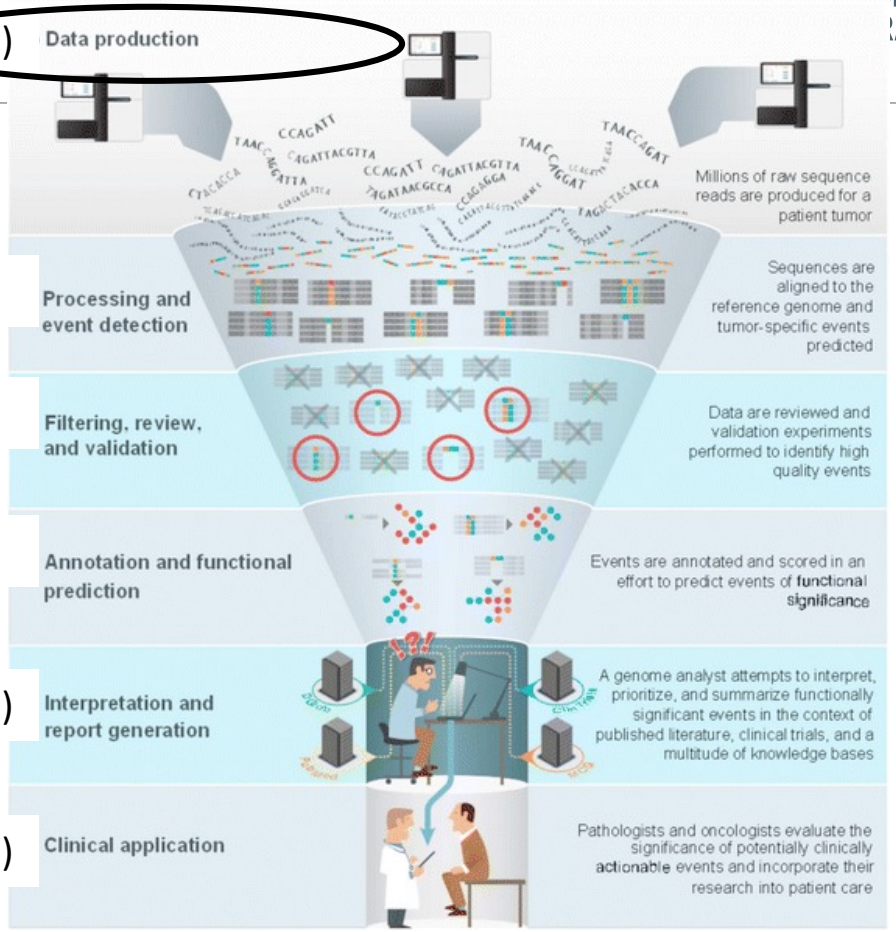

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Genetics in Medicine
Volume 24, Issue 5, May 2022, Pages 986-998

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Special Article

Standards for the classification of pathogenicity of somatic variants in cancer (oncogenicity): Joint recommendations of Clinical Genome Resource (ClinGen), Cancer Genomics Consortium (CGC), and Variant Interpretation for Cancer Consortium (VICC)

Peter Horak [1], Malachi Griffith [2], Arpad M. Danos [2], Beth A. Pitel [3], Subha Madhavan [4], Xuelu Liu [5], Cynthia Chow [6], Heather Williams [7], Leigh Carmody [8], Lisa Barrow-Laing [9], Damian Rieke [10], Simon Kreutzfeldt [1], Albrecht Stenzinger [11], David Tamborero [12], Manuela Benary [10], Padma Sheila Rajagopal [13], Cristiane M. Ida [3], Harry Lesmana [14], Laveniya Satgunaseelan [15], Jason D. Merker [16] ...Dmitriy Sonkin [35]

Standards

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Pat. *1975

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Local Resection 09/2022
TMB 3.86 Mut/Mb
HER2 0
pMMR
PD-L1 CPS 15
NTRK negative

BRAF p.V600E (AF 14%)
TP53 p.C182* (AF 39%)

Standards

Good et al. Genome Biol . 2014

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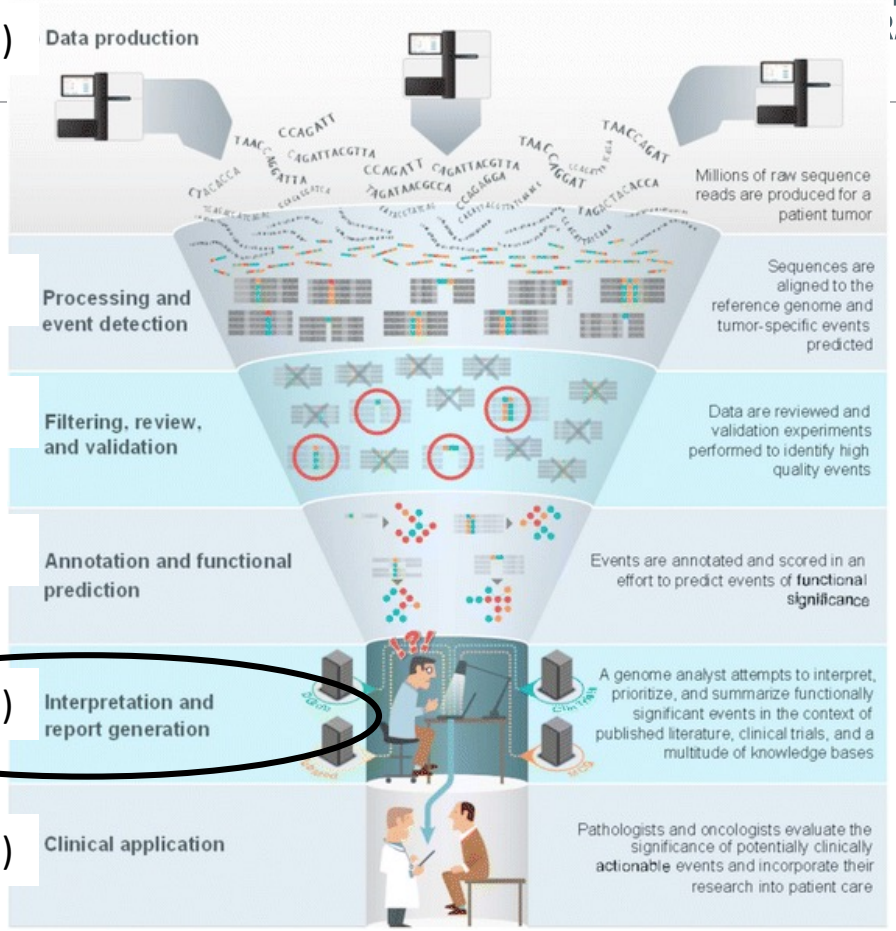

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BRAF p.V600E (AF 14%)
TP53 p.C182* (AF 39%)

Rieke et al., BMC Medicine 2022

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Standards

1. List of aberrations

- Establishment of a list of molecular aberrations independent of the type of molecular analysis (e.g. SNV, CNV, gene expression changes, immunohistochemistry…)

2. Filtering

- Preprocessing for the identification of potential biomarkers, using public databases and *in silico* algorithms

3. Annotation

- Identification of clinical relevance with structured literature search and databases using evidence levels
- Identification of diagnostic, predictive, prognostic, predisposing and pharmacogenomics biomarkers

4. Validation

- Analysis of missing data
- Validation of biomarkers if necessary
- Analysis of biomarkers in context

5. Discussion

- Interdisciplinary discussion
- Assessment of additional information

Standards

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NIH National Library of Medicine
National Center for Biotechnology Information

Log in

PubMed.gov

BRAF AND colorectal cancer

Search

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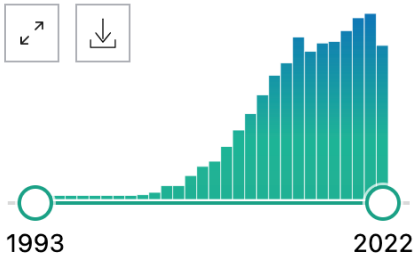
MY NCBI FILTERS

4,296 results

Page 1 of 430

RESULTS BY YEAR



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Cite

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Diagnosis and Treatment of Metastatic **Colorectal Cancer**: A Review.

Biller LH, Schrag D.

JAMA. 2021 Feb 16;325(7):669-685. doi: 10.1001/jama.2021.0106.

PMID: 33591350 Review.

IMPORTANCE: **Colorectal cancer** (CRC) is the third most common cause of **cancer** mortality worldwide with more than 1.85 million cases and 850 000 deaths annually. ...OBSERVATIONS: **Colorectal cancer** is the third most common cause of **cancer** mo ...

Griffith et al., Nat Genet. 2017
Krysiak et al., Nat Cancer. 2022
Krysiak et al., Nucleic Acids Res. 2022

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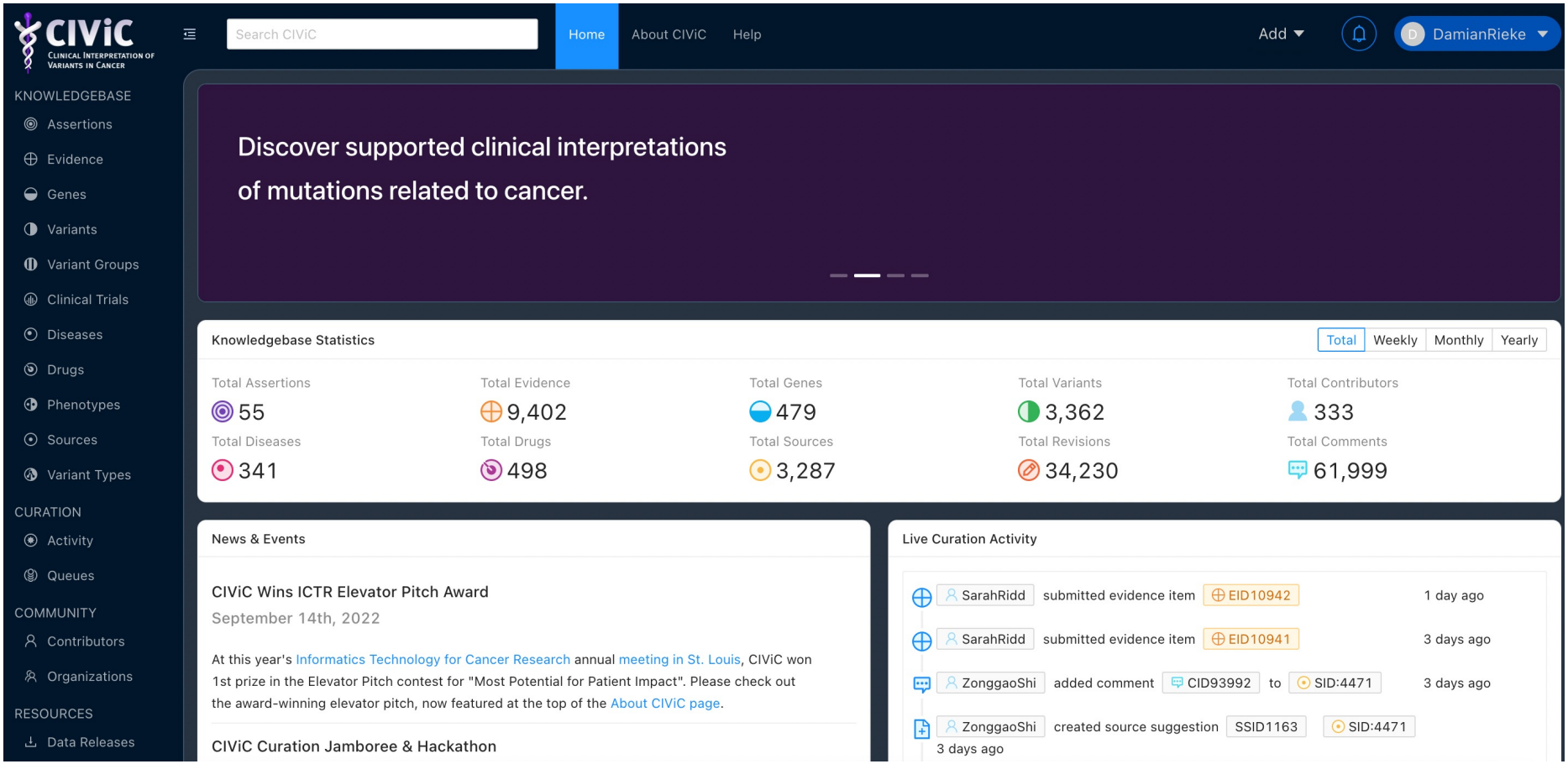
Standards



Standards

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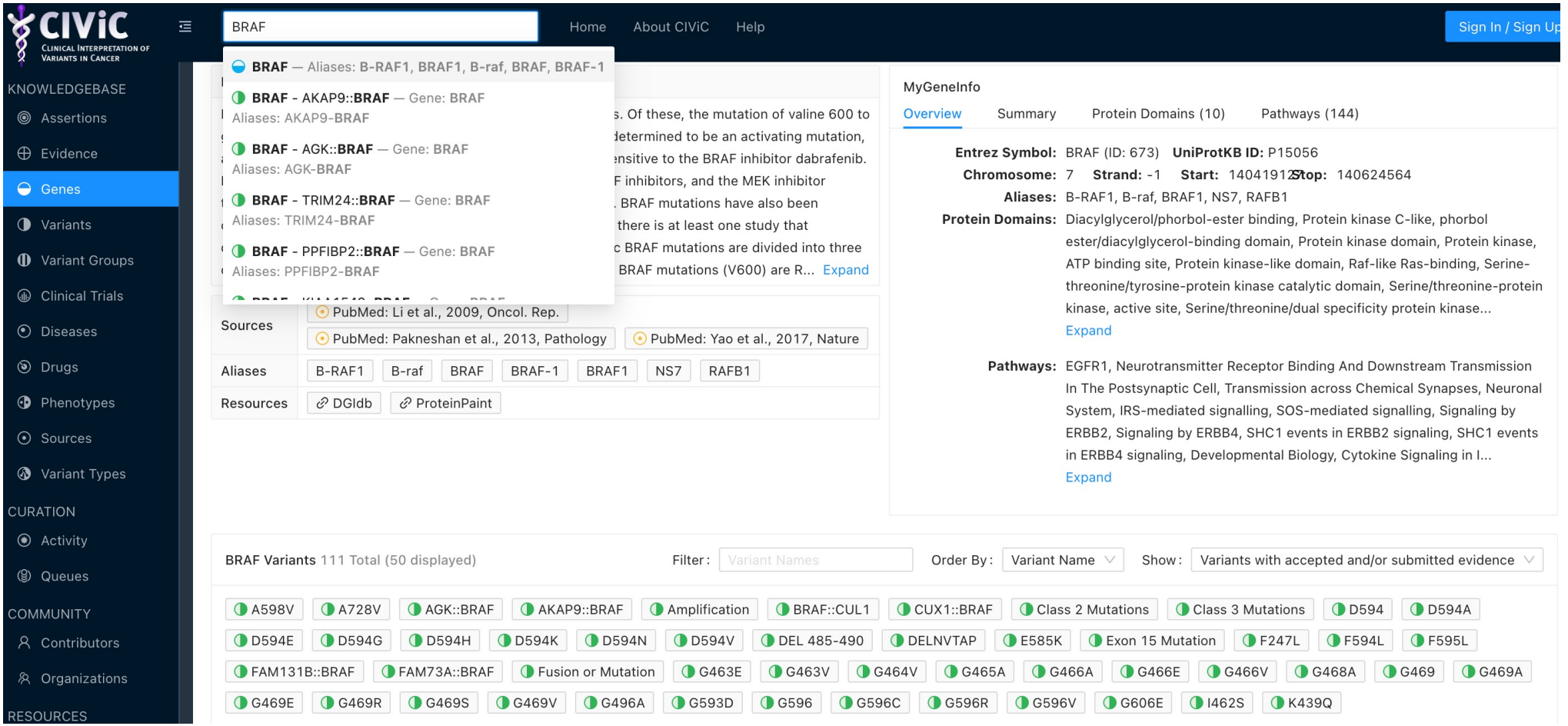

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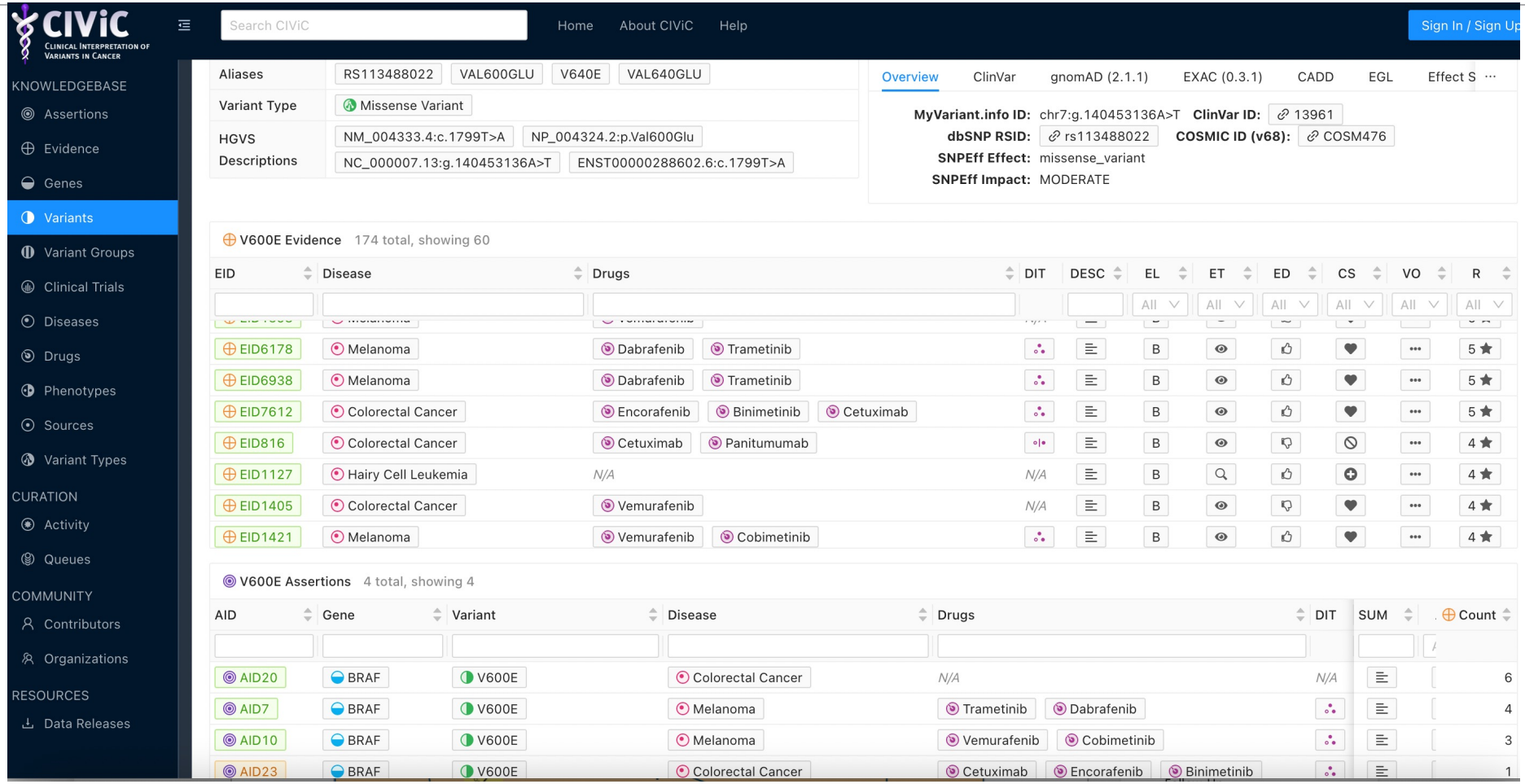

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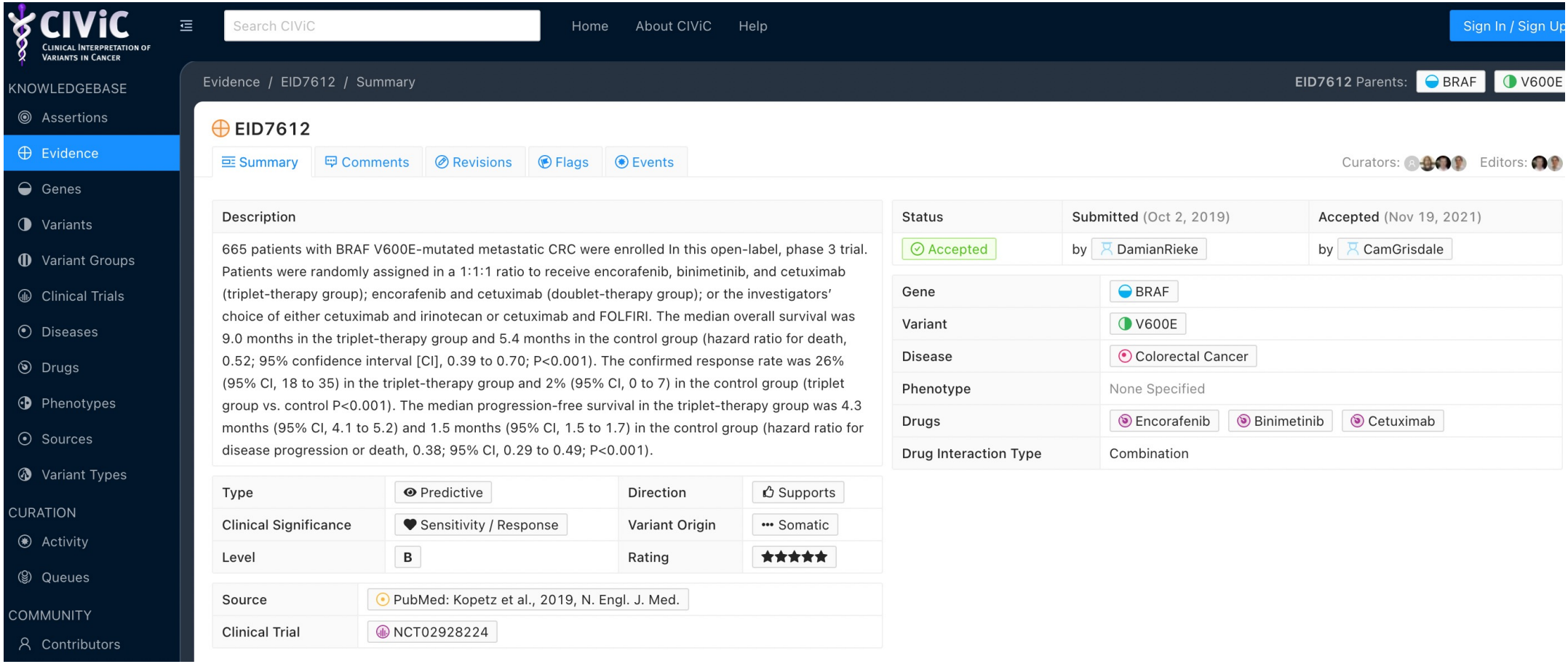

Chakravarty et al. *JCO Precision Oncology* 2017

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Standards

OncoKB™ Levels of Evidence Actionable Genes Cancer Genes API / License About News FAQ Account Memorial Sloan Kettering Cancer Center

evidence assigning their level of clinical actionability.

If you notice any mistakes or omissions, please reach out to us.

Search ...

Level	Alterations	Level-associated cancer types	Drugs	Citations
1	V600	Erdheim-Chester Disease	Vemurafenib	2
1	V600	Melanoma	Vemurafenib + Cobimetinib + Atezolizumab	1
1	V600E	All Solid Tumors (excluding Colorectal Cancer)	Dabrafenib + Trametinib	7
1	V600E	Anaplastic Thyroid Cancer	Dabrafenib + Trametinib	1
1	V600E	Biliary Tract Cancer, NOS	Dabrafenib + Trametinib	7
1	V600E	Colorectal Cancer	Encorafenib + Cetuximab	1
1	V600E	Melanoma	Dabrafenib	3
1	V600E	Melanoma	Dabrafenib + Trametinib	10
1	V600E	Melanoma	Encorafenib + Binimetinib	1
1	V600E	Melanoma	Trametinib	4
1	V600E	Melanoma	Vemurafenib	3
1	V600E	Melanoma	Vemurafenib + Cobimetinib	3
1	V600E	Non-Small Cell Lung Cancer	Dabrafenib + Trametinib	2
1	V600K	Melanoma	Dabrafenib + Trametinib	10

Standards

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https://ckb.jax.org/geneVariant/show?geneVariantId=49

						V600E-positive metastatic melanoma, with estimated OS rates of 56%, 30%, 21%, and 17% at 1, 2, 3, and 4 years, respectively (PMID: 28961848, PMID: 21639808; NCT01006980), and BRAF V600E is included on the companion diagnostic (FDA.gov).	21639808
BRAF V600E	melanoma	sensitive	Dabrafenib + Trametinib	FDA approved - On Companion Diagnostic	Actionable	In a Phase III trial (COMBI-v) that supported FDA approval, the combination of Tafinlar (dabrafenib) and Mekinist (trametinib) resulted in an improved overall survival rate at 12 months (72% vs 65%, HR=0.69, p=0.005), median progression-free survival (11.4 vs 7.3 months, HR=0.56, p<0.001), and objective response rate (64% vs 51%, p<0.001) compared to Zelboraf (vemurafenib) in melanoma patients harboring BRAF V600E or V600K (PMID: 25399551; NCT01597908).	detail... detail... 25399551
BRAF V600E	colorectal cancer	sensitive	Cetuximab + Encorafenib	FDA approved - On Companion Diagnostic	Actionable	In a Phase III (BEACON CRC) trial that supported FDA approval, Braftovi (encorafenib) and Erbitux (cetuximab) combination treatment (n=113) resulted in improved median overall survival (8.4 vs 5.4 months, HR=0.60, p<0.001), confirmed response rate (20% vs 2%, p<0.001), and median progression-free survival (4.2 vs 1.5 months, HR=0.40, p<0.001) compared to control (n=107) in patients with metastatic colorectal cancer harboring BRAF V600E (PMID: 31566309; NCT02928224).	detail... 31566309

ZPM Standard, according to
https://pct.mdanderson.org/pctService/resources/imageManager/image/loe

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Standards

Gleiche Tumorentität	**m1A**	In der **gleichen Tumorentität** wurde der prädiktive Wert des Biomarkers oder die klinischeWirksamkeit in einer **Biomarker-stratifizierten Kohorte** einer adäquat gepowerten **prospektiven Studie** oder **Metaanalyse** gezeigt.
	m1B	In der **gleichen Tumorentität** wurde der prädiktive Wert des Biomarkers oder die klinische Wirksamkeit in einer **retrospektiven Kohorte** oder **Fall-Kontroll-Studie** gezeigt.
	m1C	Ein oder mehrere **Fallberichte** in der **gleichen Tumorentität**.
Andere Tumorentität	**m2A**	In einer **anderen Tumorentität** wurde der prädiktive Wert des Biomarkers oder die klinische Wirksamkeit in einer **Biomarker-stratifizierten Kohorte** einer adäquat gepowerten **prospektiven Studie** oder **Metaanalyse** gezeigt.
	m2B	In einer **anderen Tumorentität** wurde der prädiktive Wert des Biomarkers oder die Klinische Wirksamkeit in einer **retrospektiven Kohorte** oder **Fall-Kontroll-Studie** gezeigt.
	m2C	Unabhängig von der Tumorentität wurde beim Vorliegen des Biomarkers eine **klinische Wirksamkeit** in einem oder mehreren **Fallberichten** gezeigt.
In vitro oder Tiermodell	**m3**	**Präklinische Daten** (*in vitro*-/*in vivo*-Modelle, funktionelle Untersuchungen) zeigen eine Assoziation des Biomarkers mit der Wirksamkeit der Medikation, welche durch eine wissenschaftliche Rationale gestützt wird.
Biologische Rationale	**m4**	Eine **wissenschaftliche, biologische Rationale** legt eine Assoziation des Biomarkers mit der Wirksamkeit der Medikation nahe, welche bisher **nicht durch (prä)klinische Daten** gestützt wird.

Verlauf: 01/2021 Multiviszerale Resektion 03/21-10/21 Chemotherapie mit Oxaliplatin, Capecitabin, Bevacizumab 11/21 pulmonale/hepatische Metastasierung 12/21 14x Irinotecan, 5-FU, Bevacizumab 06/22 Bevacizumab-Monotherapie 09/22 Stenose, Reoperation

Ausbreitung: pulmonal, lokal

Sampling: 09/22 lokal

IHC/MolPath: TMB 3.86 Mut/Mb. HER2 0. PD-L1 IC 20%, CPS 20. pMMR**.**

	Aberration evidence	Drug/s	Mechanism	EvL	PMIDs/NCT	VAF	Histology
BRAF p.V600E	p.V600E	Cetuximab/Encorafenib Irinotecan/Cetuximab/Vemurafenib	BRAF	M1a M1a	31566309 (1), 33503393 33356422 AIO FIRE-10 (aktuell noch nicht rekrutierend)	21%	CRC CRC
TP53 p.C180*						43%	

(1) BEACON trial. 665 Patienten nach mind. 1 vorherigen Therapielinie. Encorafenib/Cetuximab/Binimetinib mit 26% ORR, OS 9 Monate. Cetuximab/Encorafenib mit OS 8.4 Monaten. Retrospektive Analyse mit äquivalentem Ergebnis Duplette

(2) SWOG trial. 106 patients pretreated BRAF CRC. Irinotecan/Cetuximab/Vemurafenib ORR 17% vs. 4% Irinotecan/Cetuximab.

Standards

Good et al. Genome Biol . 2014

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(2) Technology selection

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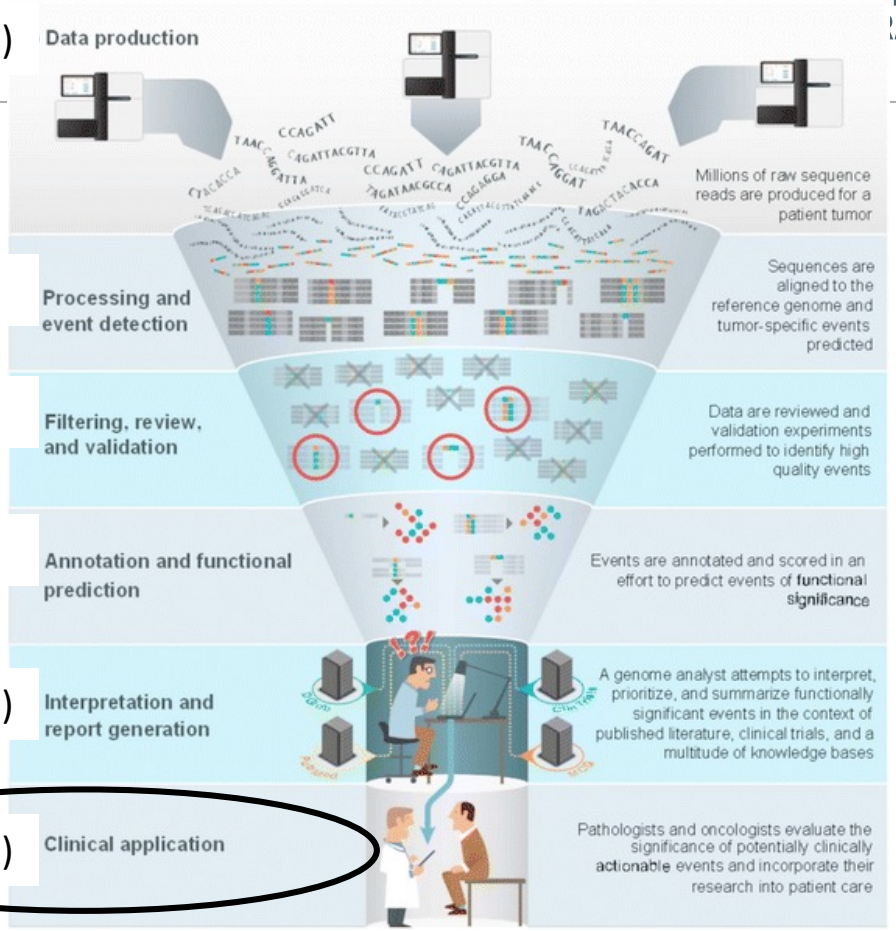

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Molekulare Tumorkonferenz

Für Patientinnen, Patienten & Interessierte

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Für Wissenschaftlerinnen & Wissenschaftler

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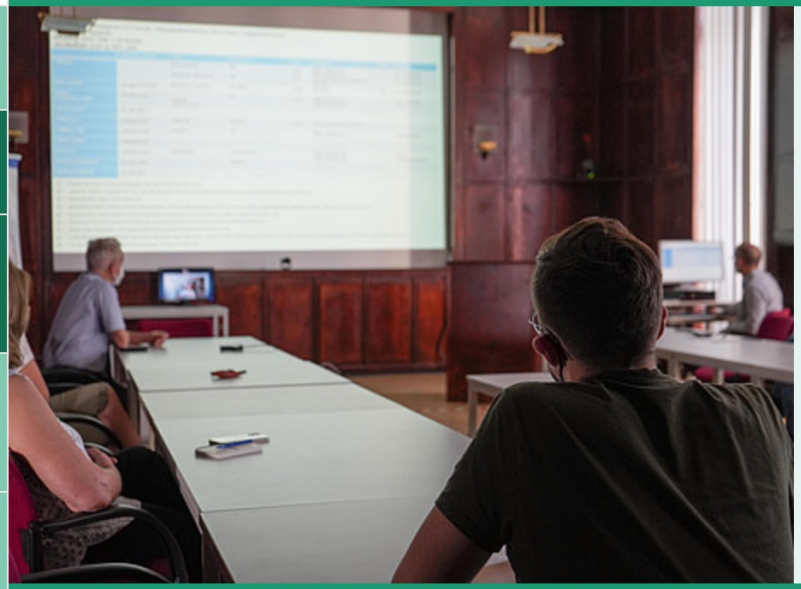

Molekulare Tumorkonferenz: Präzisionsonkologie in der klinischen Routine

In der molekularen Tumorkonferenz werden gemeinsam mit Forschern Gensequenzierungen in die Therapieentscheidung mit einbezogen.

Im Charité Comprehensive Cancer Center finden regelmäßig wöchentlich molekulare Tumorkonferenzen statt.

Durchsuchen Sie diese Website

Molekulare Tumorkonferenz: Präzisionsonkologie in der klinischen Routine

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Molekulare Tumorkonferenz:

Zusammenfassend besteht eine molekulare Rationale für
Priorität 1: Cetuximab/Encorafenib (m1a, zugelassen). Studienoption ggf. AIO FIRE-10 (aktuell noch nicht rekrutierend)

Standards

Good et al. Genome Biol . 2014

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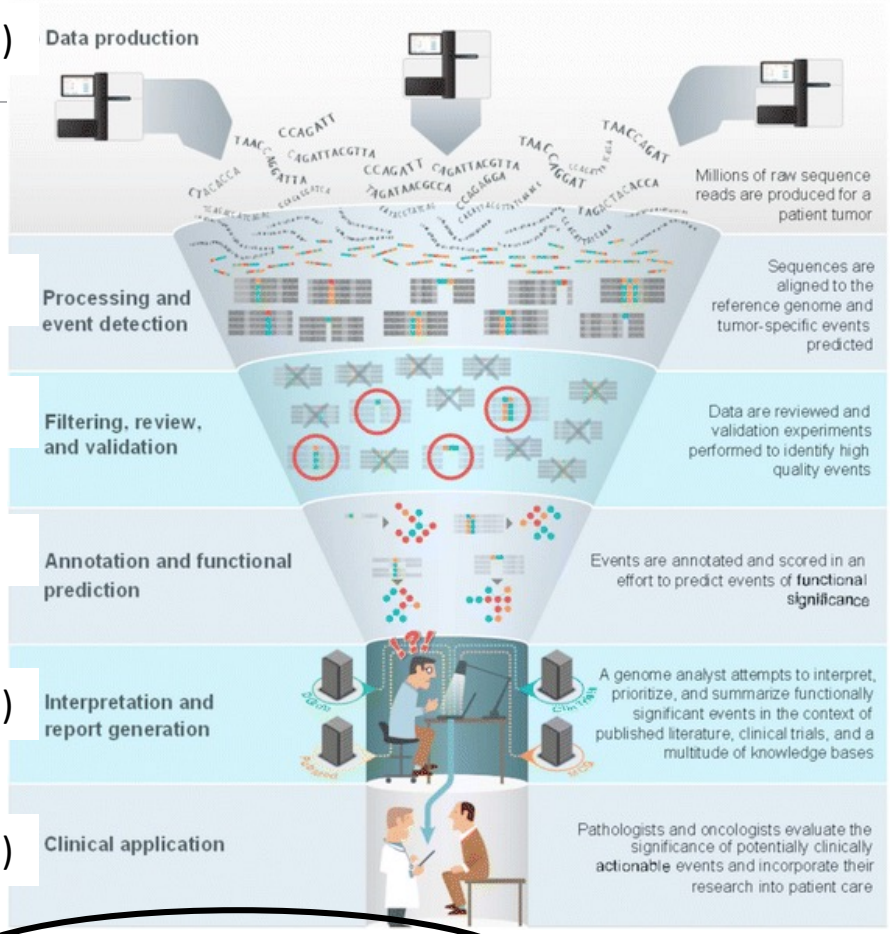

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(5)

(6) Follow-up/Trial infrastructure

Rieke et al. BMC Medicine 2022

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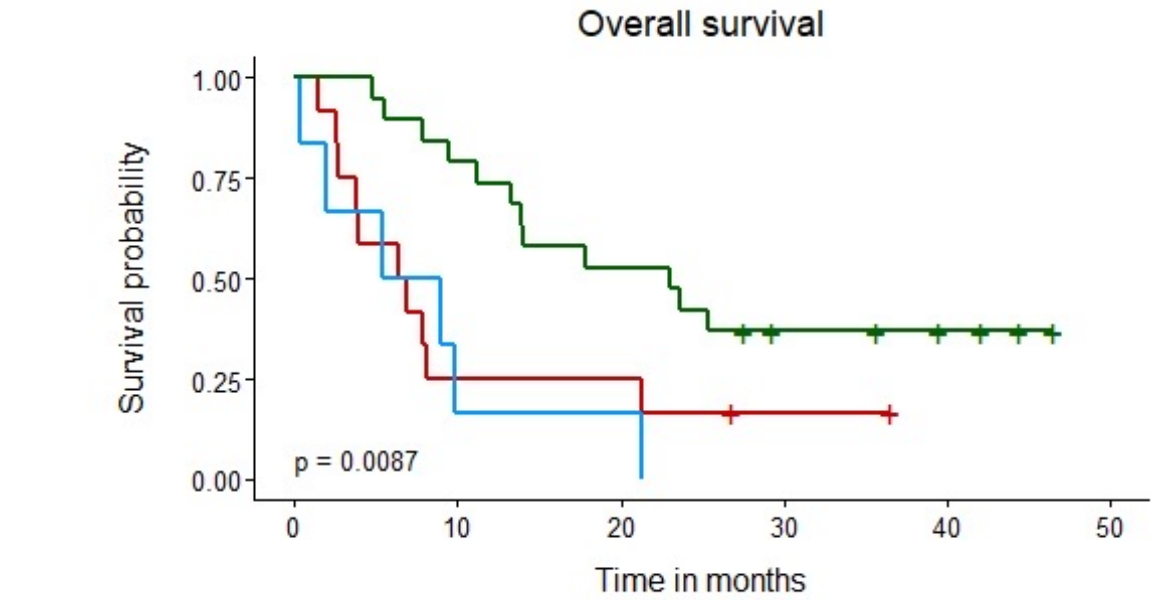
Standards



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1. **Background**
2. **Standards**
3. **Challenges**
4. Summary

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Lamping, … and Rieke. Eur J Cancer 2020

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Challenges

Publication [citation]	Matched treatment [8]	Off-label	Treated in trials	ORR [9]	SD [9]	PFS/TTF [9]	OS [9]	Other data
Zehir et al. 2017 [2]	24% (n=537)	n.r.	11% (n=527)	n.r.	n.r.	n.r.	n.r.	
Tsimberidou et al. 2014 [3]	27% (n=143)	none	100% (n=379)	12% vs. 5%	16% vs. 12%	3.9 m vs. 2.2 m	11.4 m vs. 8.6 m	
Massard et al. 2017 [4]	48% (n=199)	25% (n=50)	75% (n=149)	11%	52%	2.3 m	11.9 m	PFS2/PFS1 ≥1.3 : 33%
Burkard et al. 2017 [5]	28% (n=9)	89% (n=8)	11% (n=1)	17%	n.r.	n.r.	n.r.	
Le Tourneau et al. 2015 [6]	34% (n=99)	none	100% (n=195)	4% vs. 3%	n.r.	2.3 m vs. 2.0 m	n.r.	
Sicklick et al. 2019 [7]	49% (n=73)	none	100% (n=73)	23%	5%	3.67 m	11.8 m	PFS2/PFS1 ≥1.3: 75% vs. 36.6% in low matching score group
Rodon et al. 2019 [8]	42% (n=107)	none	100% (n=107)	11.2%	15%	2.01 m	5.9 m	PFS2/PFS >1.5: 22.4%
Tsimberidou et al. 2012 [19]	46% (n=211)	none	100% (n=352)	25% vs. 4%	23% vs. 10%	4.4 m vs. 2.3 m	11.4 m vs. 10.2 m	
Jameson et al. 2014 [20]	89% (n=29)	none	100 % (n=25)	20%	32%	n.r.	7.8 m	PFS2/PFS1 ≥1.3 : 44%
Wiesweg et al. 2013 [21]	45% (n=62)	69% (n=43)	31% (n=19)	n.r.	n.r.	n.r.	n.r.	
Jones et al. 2015 [22]	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	
Dalton et al. 2017 [23]	21% (n=28)	46% (n=11)	54% (n=13)	n.r.	n.r.	5.0 m	n.r.	
Sohal et al. 2015 [24]	22% (n=24)	38% (n=9)	50% (n=12)	n.r.	n.r.	n.r.	n.r.	
Johnson et al. 2014 [25]	21% (n=18)	39% (n=7)	61% (n=7)	22%	28%	n.r.	n.r.	
Radovich et al. 2016 [26]	100% (n=44)	none	100% (n=101)	n.r.	n.r.	2.8 m vs. 1.6 m	n.r.	PFS2/PFS1 ≥1.3 : 43.2% vs. 5.3%
Stockley et al. 2016 [27]	n.a.	none	100% (n=245)	19% vs. 9%	n.r.	n.r.	16 m vs. 13 m	any tumor shrinkage: 62% vs. 32%
Schwaederle et al. 2016 [28]	48% (n=87)	n.r.	n.r.	n.r.	n.r.	4.0 m vs. 3.0 m	12.7 m vs. 12.4 m	PFS2/PFS1 ≥1.3 : 45.3% vs. 19.3%
Von Hoff et al. 2010 [29]	79% (n=66)	n.r.	n.r.	10%	n.r.	n.r.	5 m	PFS2/PFS1 ≥1.3 : 27%
Tredan et al. 2017 [30]	11% (n=101)	n.r.	n.r.	17%	34%	2.8 m	n.r.	
Cobain et al. 2017 [31]	n.a.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	
Hoefflin et al. 2018 [32]	32% (n=33)	67% (n=22)	6% (n=2)	33%	24%	n.r.	not reached	PFS2/PFS1 ≥1.3 (off label): 57.1%
Basse et al. 2018 [33]	10% (n=45)	n.a.	100% (n=45)	11%	n.a.	n.a.	n.a.	
median	**34%**	**46%**	**100%**	**17% [10]**	**24% [10]**	**3.2 m [10]**	**11.4 m [10]**	

Lamping, … and Rieke. Eur J Cancer 2020

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Challenges

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Challenges

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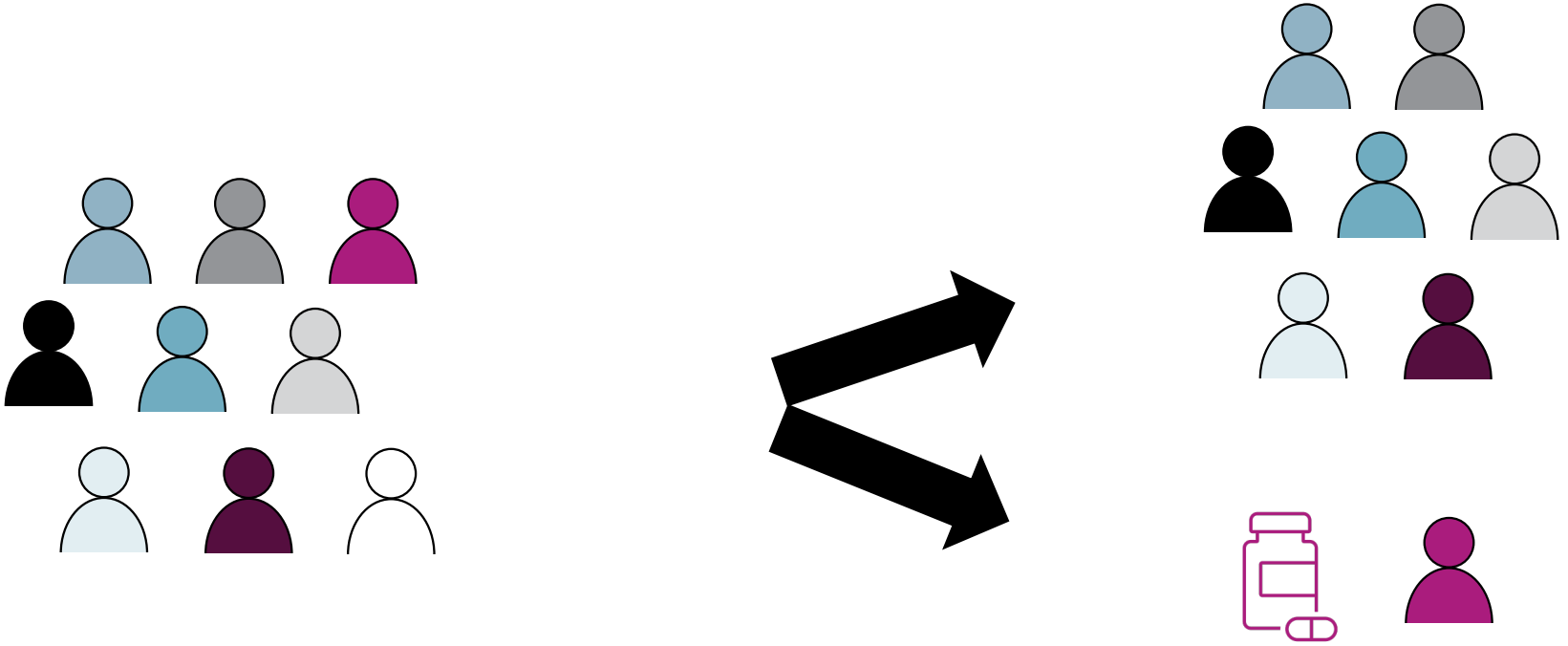

Rieke et al., JCO Precis Oncol 2018

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Challenges

Table 1. Sample Patients as Provided to the Molecular Tumor Boards

Patient	Clinical Information	Additional Information	Sequencing	Fusion Genes	Copy No.	Gene Expression
1. 56-year-old patient	Initial diagnosis October 2014: TTF1-positive lung adenocarcinoma T3N3M0 (UICC IIIB) with negative *ALK/ROS* translocation and negative *EGFR* mutation status. Definite chemoradiotherapy. Widespread metastases to the peritoneum diagnosed in Nov 2015. Progressive after platinum-based chemotherapy and PD-1 inhibition (nivolumab). ECOG 1.	Tumor specimen from diagnostic mediastinoscopy Oct 2014: 25% tumor content, 580× mean sequencing depth.	Panel sequencing: *KRAS* G13D, *TP53* A276G, *PTPRS* R238*, *ZFHX3* F2994L, *CDH1* D433N	N/A	N/A	N/A

Rieke et al., JCO Precis Oncol 2018

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Challenges

Table 3. Treatment Recommendations as Provided by the Respective Molecular Tumor Boards for Patient 1

Tumor Board	Recommendation	Provided Rationale	Additional Recommendation
1	Pan-Raf inhibitor	Downstream effect *KRAS* mutation	
2	No targeted therapy		*MET* and *RET* testing
3	Clinical trial for *KRAS* mutation	*KRAS* mutation	Genetic counseling for *CDH1* and *TP53* mutations (potential germline mutation)
4	Sorafenib clinical trial	*KRAS* mutation	
5	Docetaxel and selumetinib	*KRAS* mutation (data from phase II clinical trial)	Genetic counseling (*CDH1* mutation; potential germline mutation)
6	N/A because of missing information		

NOTE. Rationales were provided for only some of the recommendations and asked for if missing initially.
Abbreviations: N/A, not available; RET, Ret proto-oncogene.

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Challenges

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Table 3. Treatment Recommendations as Pro...

Tumor Board	Reco...
1	
2	
3	
4	
5	L... ...seling (*CDH1* mutation; ...tential germline mutation)
6	N/... info

NOTE. Ration... ...some of the recommendations and asked for if missing initially.
Abbreviations: N... ...ble; RET, Ret proto-oncogene.

FDA NEWS RELEASE

FDA Approves First Targeted Therapy for Lung Cancer Mutation Previously Considered Resistant to Drug Therapy

Share Tweet LinkedIn Email Print

www.fda.gov

For Immediate Release: May 28, 2021

Challenges

dnpm Deutsches Netzwerk für Personalisierte Medizin

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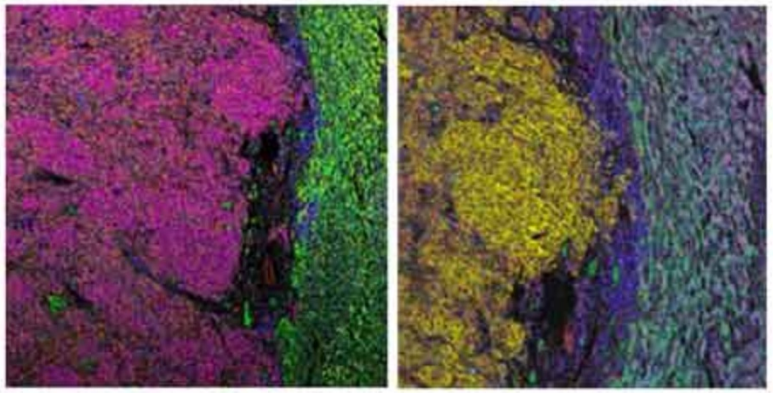
- Leistungen
- **Plattform für personalisierte Krebsmedizin der Charité (PPK-C)**
- Molekulare Tumorkonferenz
- Präzisionsonkologische Sprechstunde
- AG klinische und translationale Präzisionsonkologie | Research group - Clinical and translational precision oncology
- Für Patientinnen, Patienten



Fotos: Prof. Klauschen
Treat2oplus program, using HYPERION technology,
Yaspo Lab at Max Planck Institute for Molecular Genetics, Berlin

Plattform für personalisierte Krebsmedizin der Charité (PPK)

Krebs ist eine Erkrankung des Erbguts und seiner Signalwege. Dabei gilt: So einzigartig wie jeder:e Patient:in ist, ist auch dessen Krebserkrankung. In der Präzisionsonkologie tragen wir diesem Umstand bestmöglich Rechnung.

Durchsuchen Sie diese Website

Startseite › Leistungen › Plattform für personalisierte Krebsmedizin der Charité (PPK-C)

Präzisionsonkologie am Charité Comprehensive Cancer Center

Challenges

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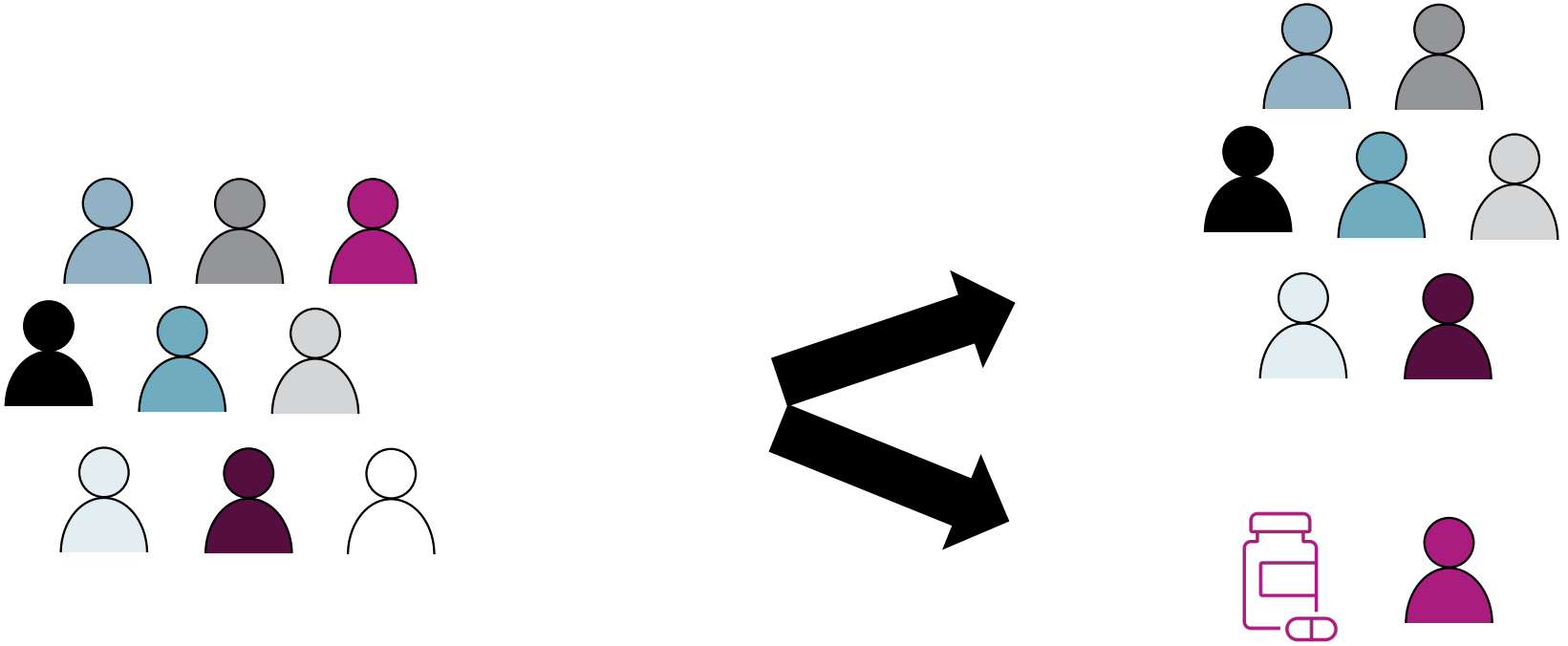

Challenges

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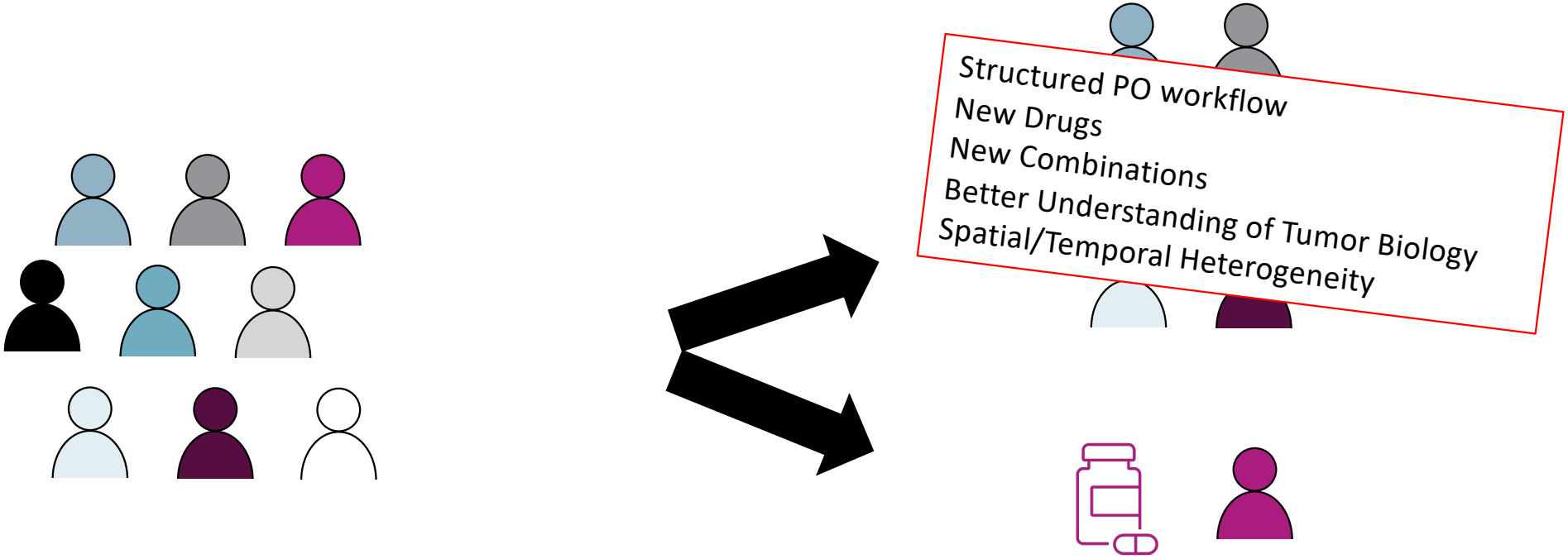

CONTENT

1. Background
2. Standards
3. Challenges
4. **Summary**

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Summary

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- **Multi-Step Process**
- **Integration of novel analyses, treatments, combinations**
- **Integration of complex data and multiple data layers**
- **Clinico-genomic database for research use**

Comprehensive Cancer Center
Ulrich Keilholz
Stefanos Bamopoulos
Manuela Benary
Elisabeth Vinis
Anna Klostermann
Yvette Jegodka
Mario Lamping
Till de Bortoli
Ivan Jelas
Serge Leyvraz
Gina Rüter
Johannes Berger
Michael Ruschel
Thomas Cramer
Philipp Euskirchen
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Konrad Klinghammer
Ben von der Emde
Ulrich Keller/Sebastian Stintzing/Lars Bullinger

DKTK/DKFZ Heidelberg
Peter Horak
Stefan Fröhling

Core Unit Bioinformatics BIH
Dieter Beule
Eric Blanc
Erika Zuljan

VICC Consortium
Griffith Lab St. Louis

(Molecular) Pathology
Markus Möbs
Maria Joosten
Wolfgang Schmitt
David Horst

Humangenetik
Claus-Erik Ott
Stefan Mundlos

Radiologie
Tobias Penzkofer
Bernd Hamm

…

THANK YOU!

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Berliner Krebsgesellschaft e.V.
Deutsches Konsortium für translationale Krebsforschung

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