curadigm
Data to Insights

CASE STUDY

Actionable mutations for selection of targeted therapy in Oncology

Objective

The customer wanted to develop and expand a biomarker template that could report molecular tests for cancer synoptically. In addition, the customer was interested in determining the utility of biomarker templates based on a range of end users, including surgical pathologists and medical oncologists.

Scope of the project

The initial aim was to create a Proof-of-Concept, which involved creating data templates, biomarker ontologies, and creating a list of high-priority predictive biomarkers. As part of the project scoping, a data template was created after a series of discussions with the client and end users (pathologists/medical oncologists), and critical data points were finalized. Based on the Regulatory approval, NGS panels, the top priority biomarkers (actionable mutations) were selected.

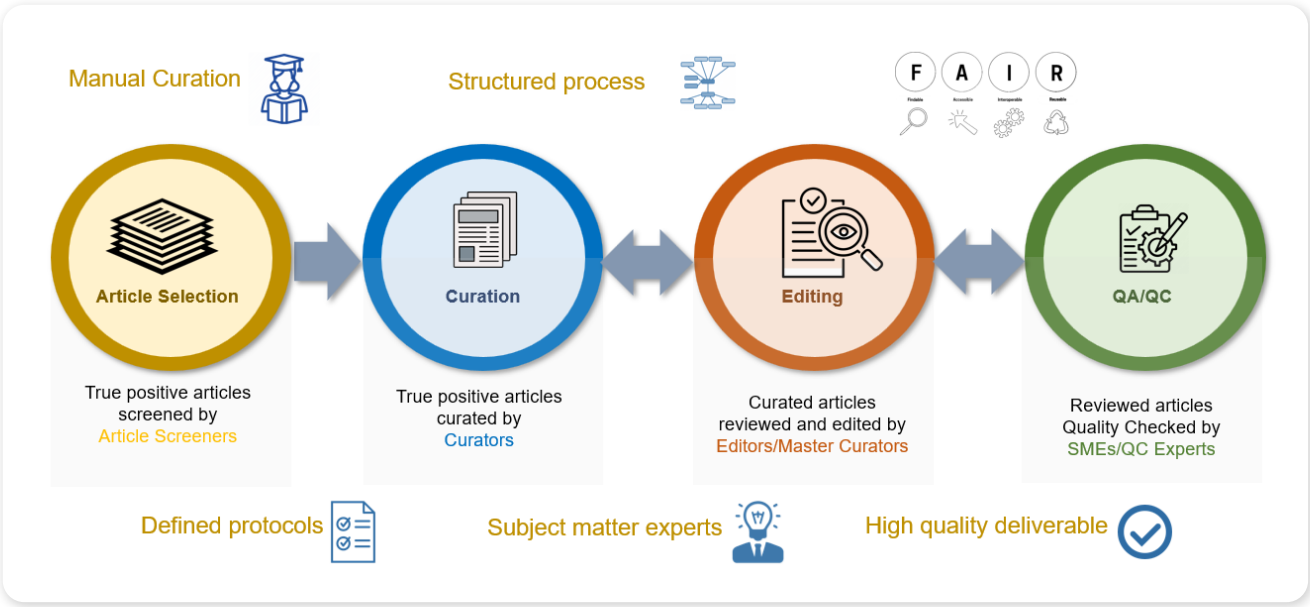
FDA approved biomarkers, CLIA approved biomarkers, NCCN/EDRN guidelines, NGS panels, and biomarkers that have been studied in literature or publications were used to determine the Biomarker Priority List. The expert panel (Pathologists/Oncologists) consistently reviewed and approved the prioritization. The evidence-based tier system was adopted as defined by ACMG guidelines.

Search strategy

Curadigm used multiple search strategies to screen for biomarkers (genes) related to the cancer type. Search parameters were constantly optimized as the curation progressed.

Curation Process

We emphasize high quality deliverable through two level QC approach



Results

Gene	Biomarker	Variant type	Clinical significance	Drug Class	Interpretation	Selected Publications	Evidence Level	Census tiers
EGFR	EGFR Exon 19 Deletion	Inframe Deletion	Sensitivity/Response; Resistance	Tyrosine kinase inhibitor; Immune	NSCLC patients with exon 19	24868098; 23982599; 1	A - Validated; B - Clinical	*Tier 1-Level A; *Tier 1-Level B
EGFR	L858R	Missense Variant	Sensitivity/Response; Resistance	Tyrosine kinase inhibitor; Immune	Presence of EGFR L858R m	24868098; 23982599; 2	A - Validated; B - Clinical	*Tier 1-Level A; *Tier 1-Level B
EGFR	T790M	Missense Variant	Sensitivity/Response; Resistance	Tyrosine kinase inhibitor	T790M-positive advanced NS	27959700; 26729184; 2	A - Validated; B - Clinical	*Tier 1-Level A; *Tier 1-Level B
EGFR	A763_Y764insFQEA	Inframe Insertion	Sensitivity/Response	Tyrosine kinase inhibitor	NSCLC patients harbouring E	24353160	B - Clinical	*Tier 1-Level B
EGFR	EGFR Amplification	[NA]	Sensitivity/Response	Tyrosine kinase inhibitor	NSCLC patients with EGFR (	20826716; 27664271; 2	B - Clinical	*Tier 1-Level B
EGFR	C797S	Missense Variant	Resistance	Tyrosine kinase inhibitor	Acquired EGFR C797S muta	25939061	B - Clinical	*Tier 1-Level B
EGFR	E746_T751delinsA	Deletion/Insertion variat	Sensitivity/Response	Tyrosine kinase inhibitor	Lung cancer patients with EG	15870435;15118072;20	B - Clinical	*Tier 1-Level B
EGFR	EGFR Exon 20 Insertion	Inframe Insertion	Sensitivity/Response; Resistance	Tyrosine kinase inhibitor	Majority of patients with adva	26051236; 26096453	B - Clinical	*Tier 1-Level B
EGFR	G719S	Missense Variant	Sensitivity/Response	Tyrosine kinase inhibitor	NSCLC patients harbouring E	26124334	B - Clinical	*Tier 1-Level B
EGFR	G719X	Missense Variant	Sensitivity/Response	Tyrosine kinase inhibitor	NSCLC patients with EGFR (	31825714	B - Clinical	*Tier 1-Level B
EGFR	Gain-of-function	[NA]	Sensitivity/Response	Tyrosine kinase inhibitor	Patients with non-small-cell lu	15118073	B - Clinical	*Tier 1-Level B
EGFR	L861Q	Missense Variant	Sensitivity/Response	Tyrosine kinase inhibitor	NSCLC patients with EGFR (	31825714	B - Clinical	*Tier 1-Level B
EGFR	RARE Exon 18-21 mutatio	[NA]	Sensitivity/Response	Tyrosine kinase inhibitor	NSCLC patients with uncomr	21531810	B - Clinical	*Tier 1-Level B
EGFR	S768I	Missense Variant	Sensitivity/Response	Tyrosine kinase inhibitor	Lung adenocarcinoma patien	31825714; 19060236; 1	B - Clinical	*Tier 1-Level B
EGFR	S768N	Missense Variant	Resistance	Tyrosine kinase inhibitor	The first reported EGFR S76	19786660	B - Clinical	*Tier 1-Level B
EGFR	Y1092 (1068) PHOSPHOR	[NA]	Sensitivity/Response	Tyrosine kinase inhibitor	Phosphorylation of Y1068 (1(	22901364	B - Clinical	*Tier 1-Level B
EGFR	Exon 18 Overexpression	[NA]	Sensitivity/Response	Tyrosine kinase inhibitor	In patients with untreated met	24039832	B - Clinical	*Tier 1-Level B
EGFR	G719A	Missense Variant	Sensitivity/Response	Tyrosine kinase inhibitor	Advanced NSCLC patient ha	32969527	C - Case study	*Tier 2-Level C
EGFR	K806E	Missense Variant	Sensitivity/Response	Tyrosine kinase inhibitor	NSCLC patient with K806E n	21531810	C - Case study	*Tier 2-Level C
EGFR	R831H	Missense Variant	Sensitivity/Response; Resistance	Tyrosine kinase inhibitor	Chemotherapy-naive stage III	24376723; 18509184	C - Case study	*Tier 2-Level C
EGFR	G719D	Missense Variant	Sensitivity/Response	Tyrosine kinase inhibitor	Patients with stage IV lung ad	21531810	C - Case Study	*Tier 2-Level C
EGFR	H773_V774insH	Inframe Insertion	Sensitivity/Response	Tyrosine kinase inhibitor	A lung adenocarcinoma patie	24353160	C - Case Study	*Tier 2-Level C

Fewer important data fields are presented above

Biomarker	V600E	G469R	G469V	G596V
Clinical Significance	Sensitivity/Response	Sensitivity/Response	Sensitivity/Response	Sensitivity/Response
Regulatory Approval	Approved	Emerging/Novel	Emerging/Novel	Emerging/Novel
Variant Origin	Somatic	Somatic	Somatic	Somatic
Evidence Level	Tier 1-Level A	Tier 2-Level C	Tier 2-Level C	Tier 2-Level C
PubMed	27283860	26237499	27388325	26200454
Clinical Trials	NCT01336634 (P-2) NCT02091141 (P-2)			
Drug Class	Kinase inhibitor	Kinase inhibitor	Kinase inhibitor	Kinase inhibitor
Therapy Interpretation	A stage IV lung adenocarcinoma patient harboring a BRAF V600E mutation was associated with response and sensitivity to kinase inhibitor monotherapy.	Case report of a patient with NSCLC and BRAF G469R mutation who showed a dramatic response to Multi-kinase inhibitor	Case report of a patient with HCC and NSCLC (only NSCLC harboring the BRAF G469V mutation). Multi-kinase inhibitor at standard dosage led to a partial response in the primary lesion of the lung, complete response of the metastasis in the contralateral lung, and stability of HCC.	In a retrospective study of 35 lung adenocarcinoma patients (chemotherapy previously administered in 86% of patients), a patient harboring a BRAF G596V mutation was associated with partial response to Kinase inhibitor monotherapy.

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