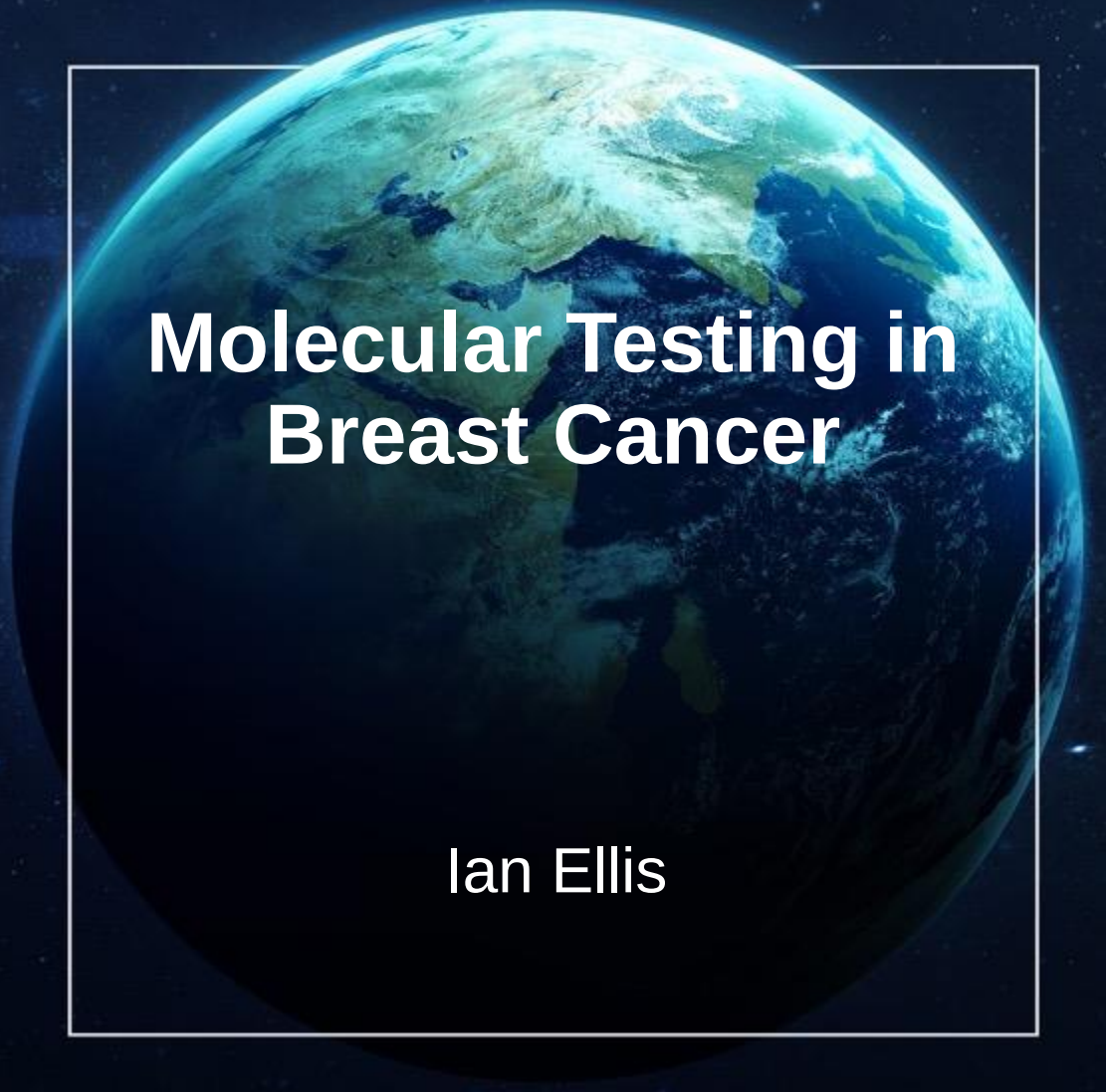
University of Nottingham
UK | CHINA | MALAYSIA



Molecular Testing in Breast Cancer

Ian Ellis

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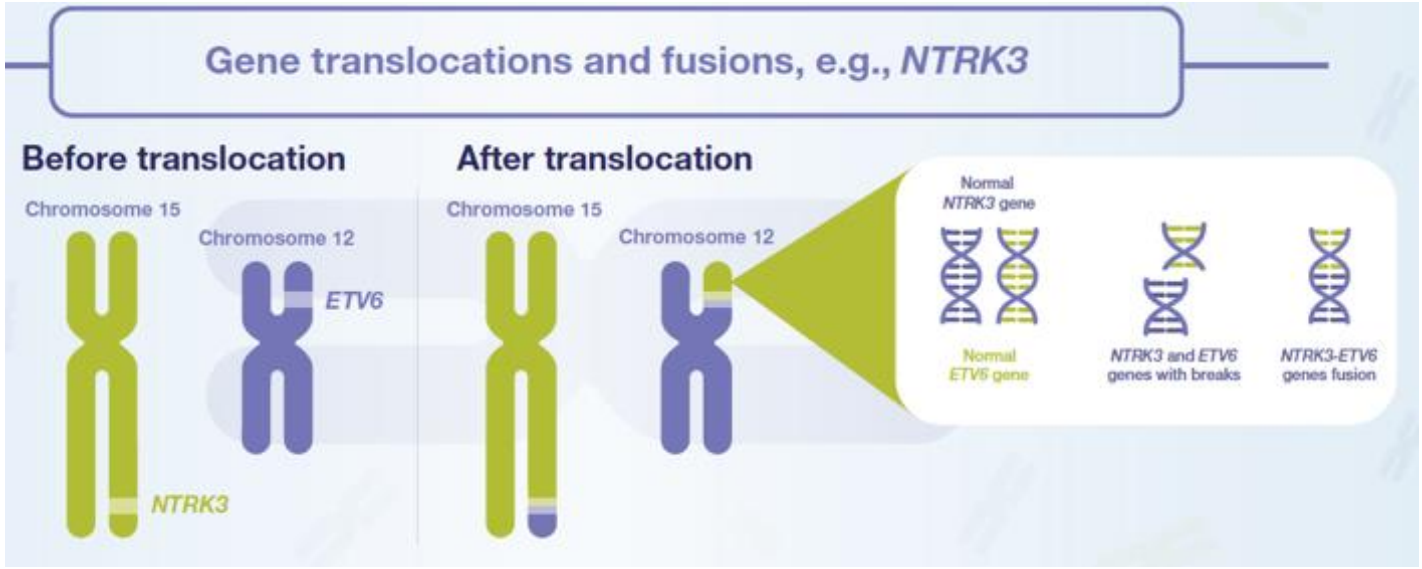
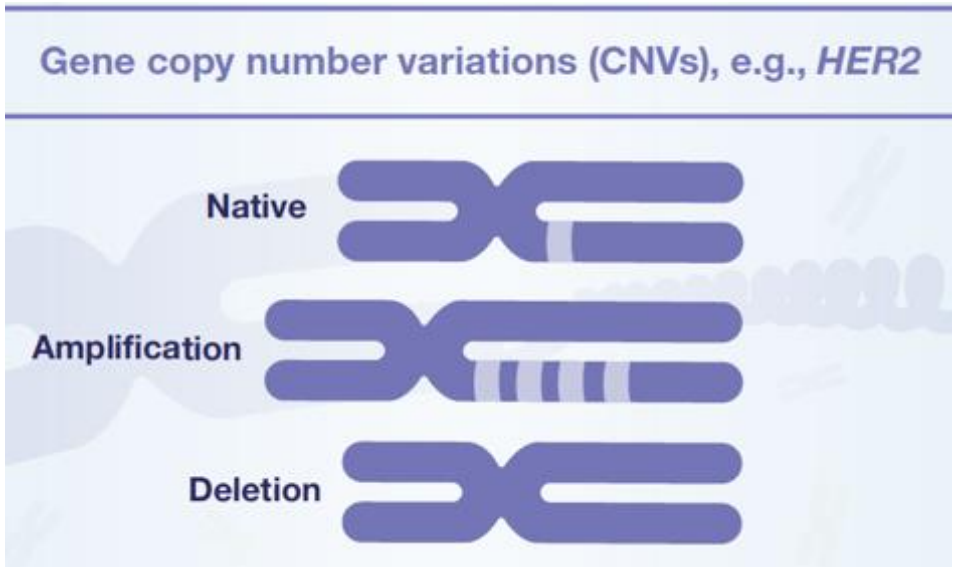
Molecular Testing in Breast Cancer

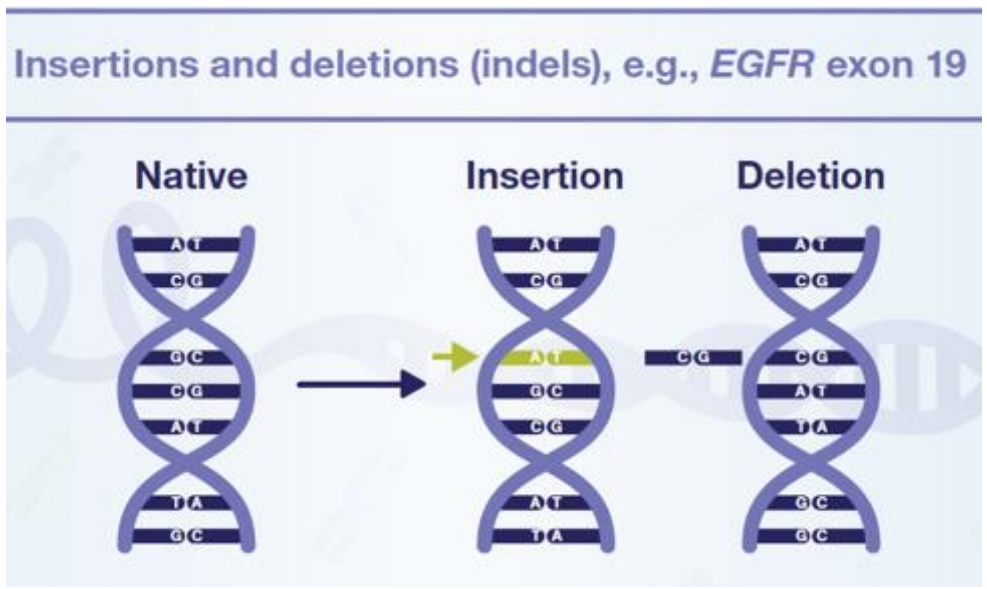
Cancer is a Disease of the Genome Caused by its Alterations

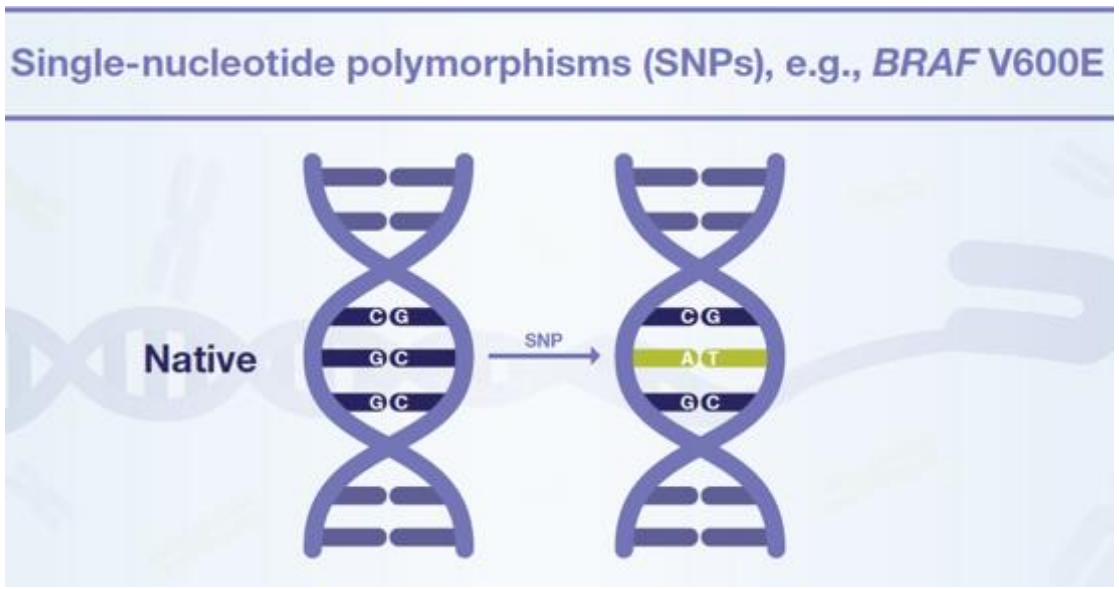
An effective and efficient tool is required to interrogate the alterations that cause cancer

Molecular Alterations in Cancer

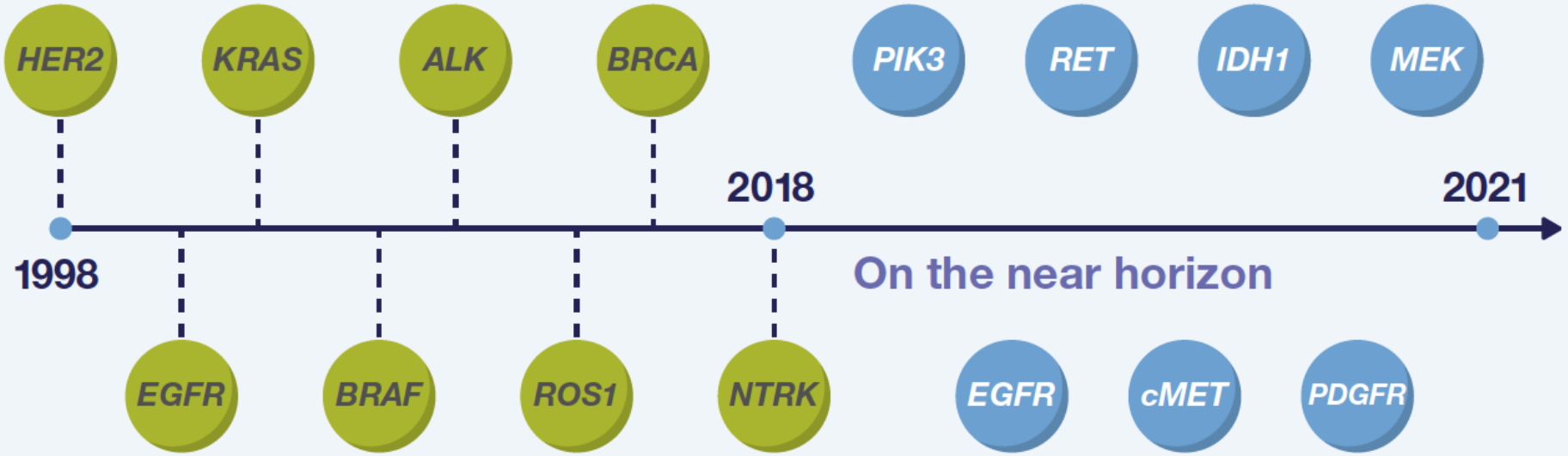


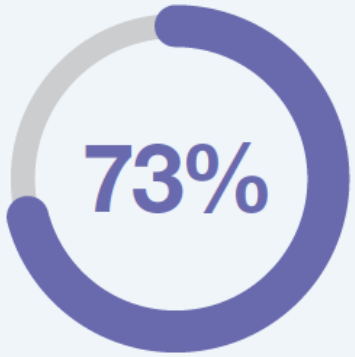






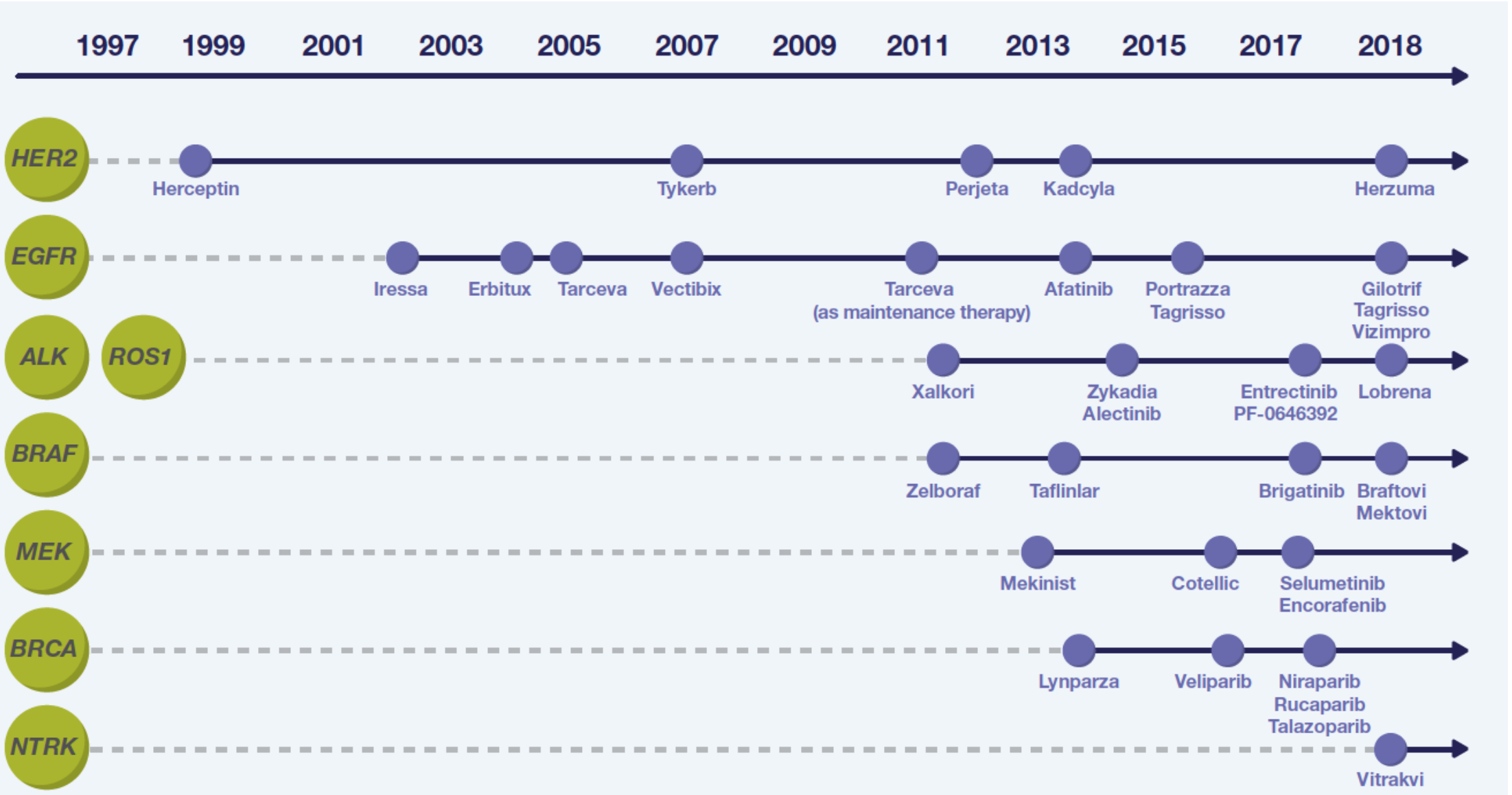
Biomarker development is accelerating



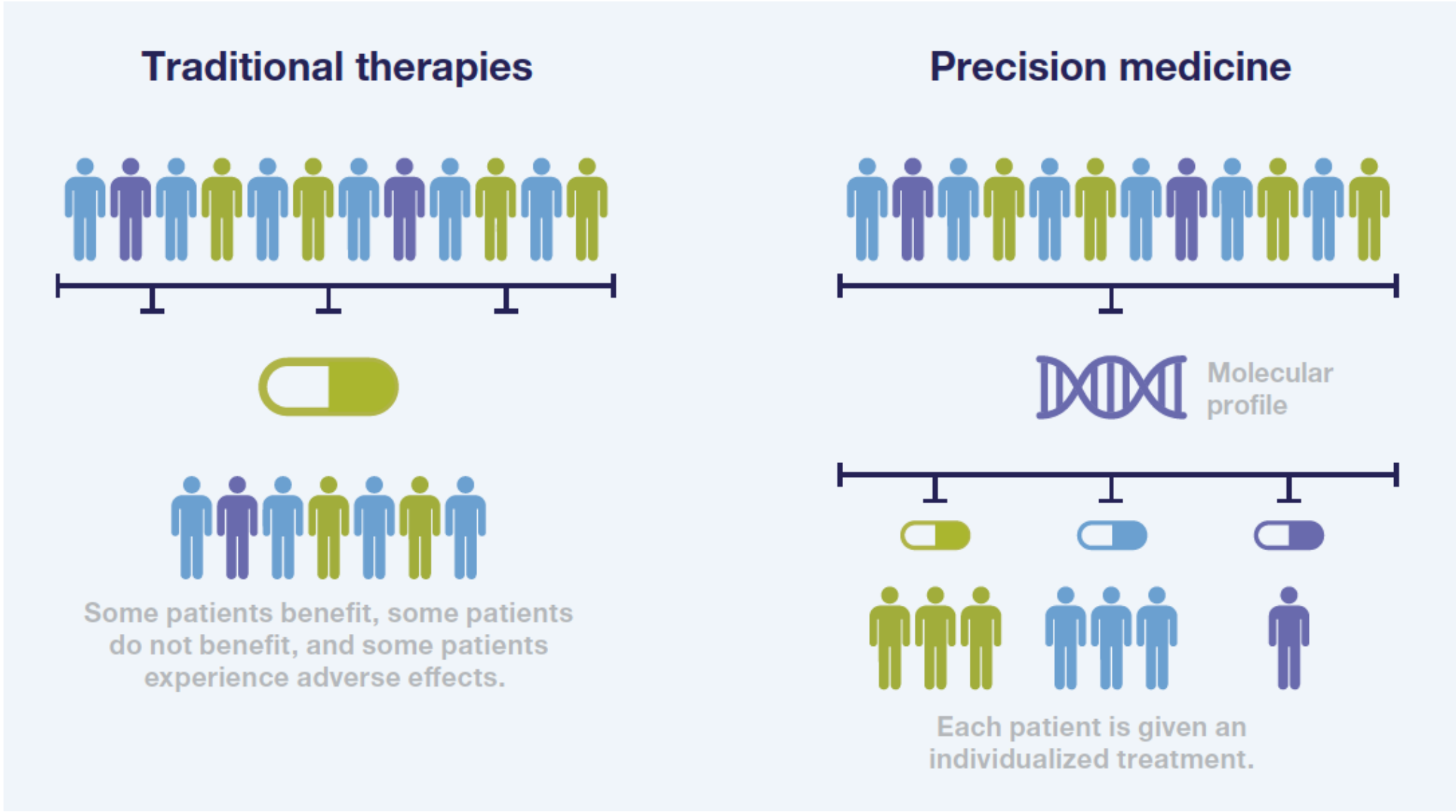


73% of medicines in oncology pipelines have associated biomarkers

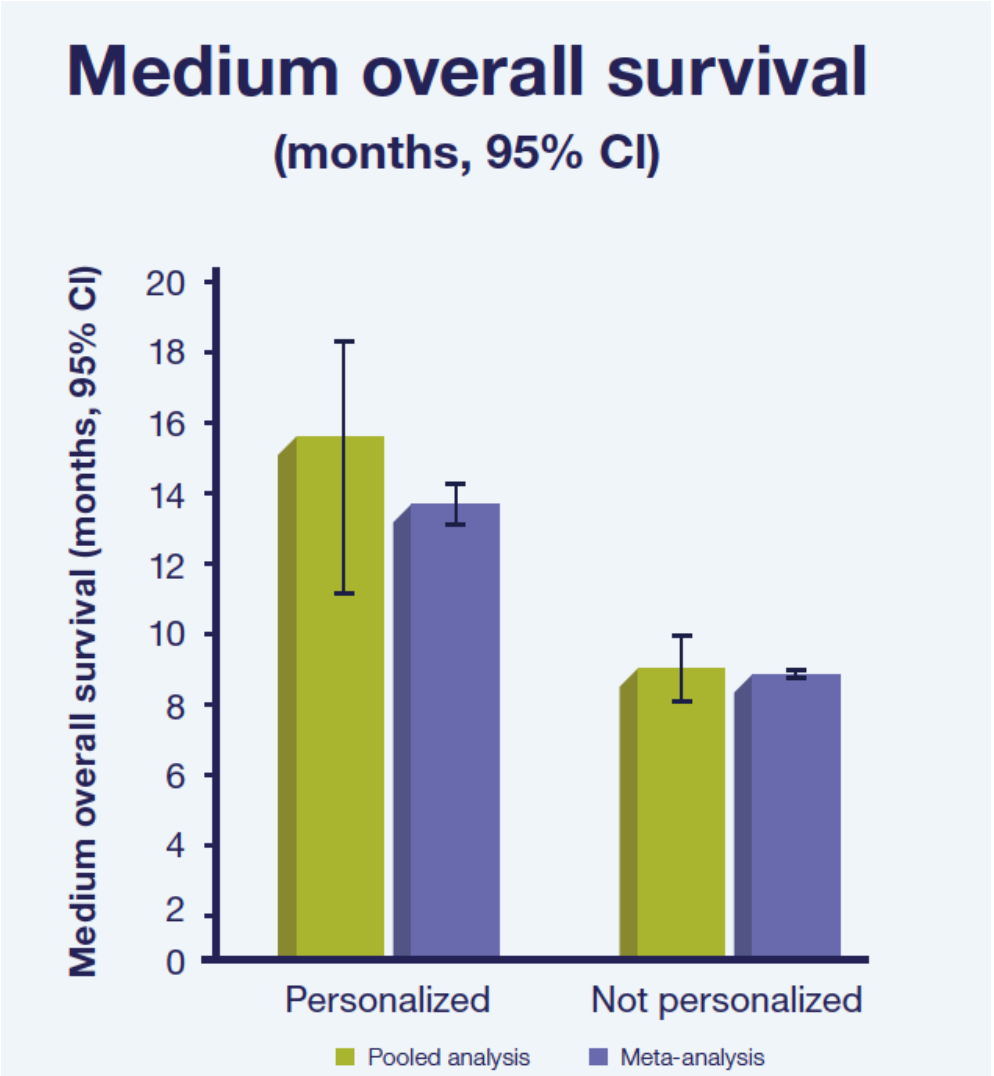
Available targeted medicines – Solid tumours



Precision medicine is enabled by molecular profiling



Precision oncology helps improve patient outcomes

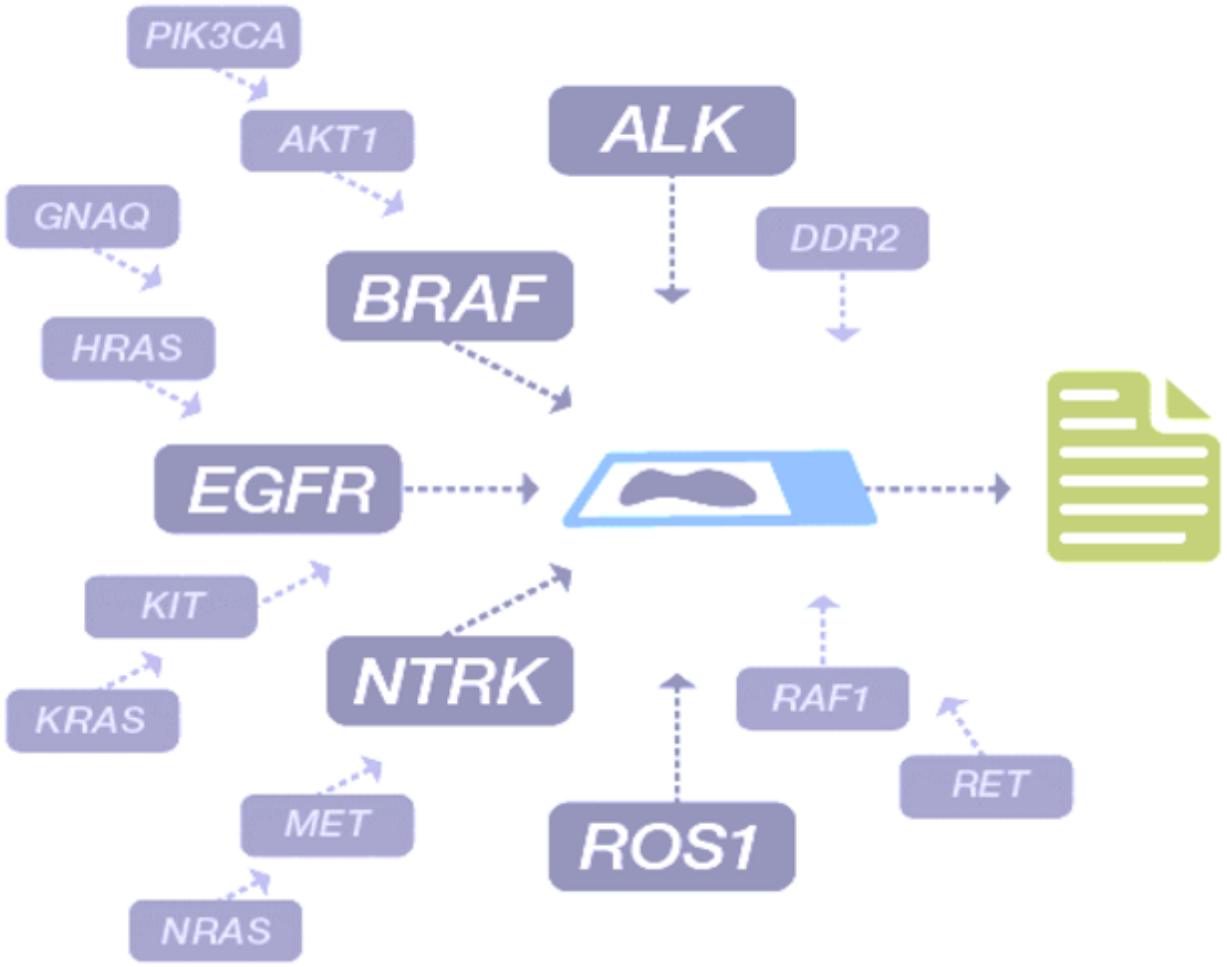


Impact of Precision Medicine in Diverse Cancers: A Meta-Analysis of Phase II Clinical Trials *J Clin Oncol*. 2015 Nov 10; 33(32): 3817–3825. 24. doi: 10.1200/JCO.2015.61.5997.

Molecular Testing in Cancer

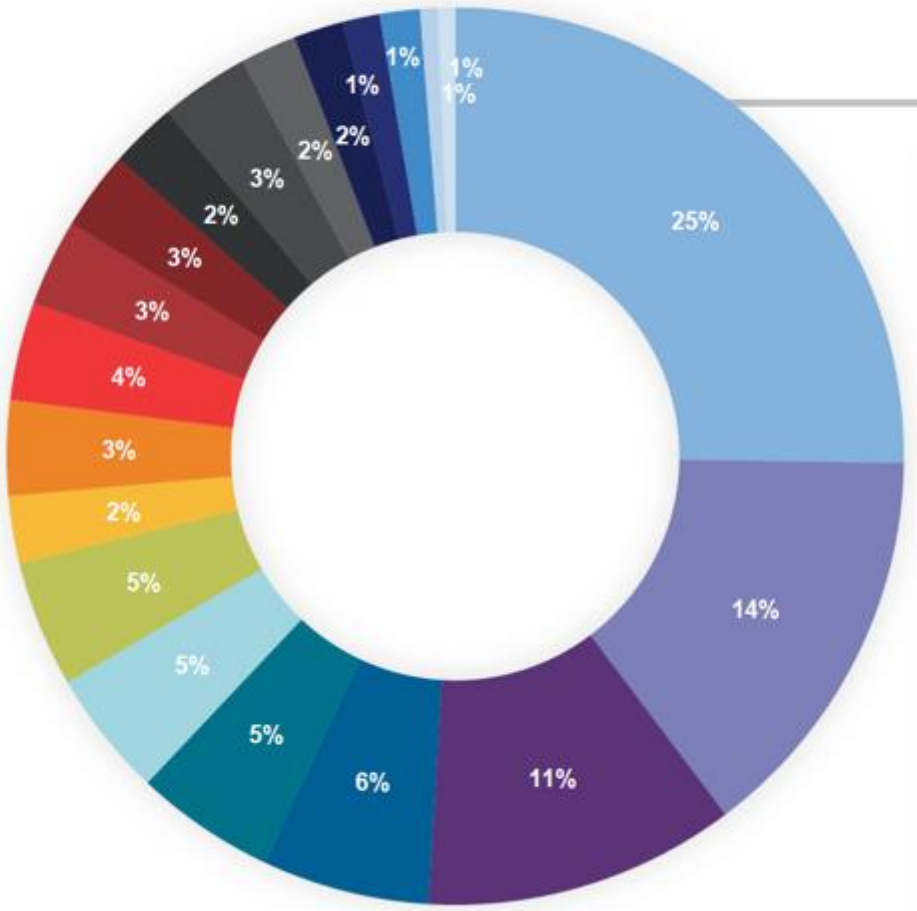
NGS is a Foundation of Precision Oncology Clinical Research

NGS can detect many different types of biomarkers simultaneously from a single sample



Molecular Testing in Breast Cancer

Pan-Cancer Clinical Research Application of OPA



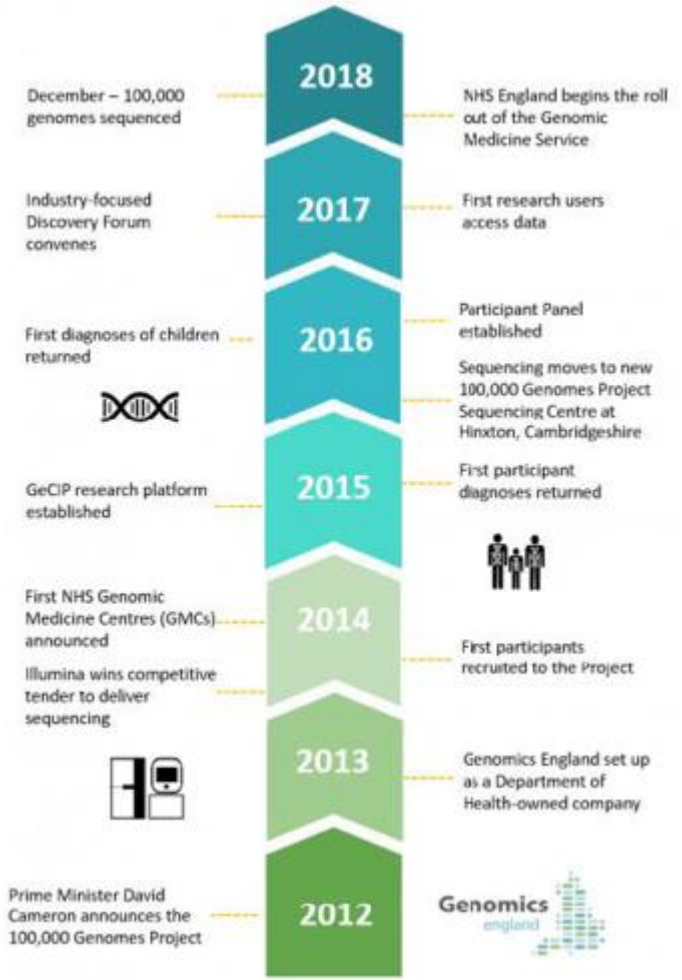
- Non-Small Cell Lung Cancer
- Breast Cancer
- Melanoma
- Gastric Cancer
- Bladder Cancer
- Head and Neck Cancer
- Pancreatic Cancer
- Thyroid Cancer
- Soft Tissue Sarcoma
- Small Cell Lung Cancer
- Unspecified Solid Tumor
- Colorectal Cancer
- Kidney Cancer
- Ovarian Cancer
- Esophageal Cancer
- Endometrial Cancer
- Liver Cancer
- Glioblastoma
- Gastrointestinal Stromal Tumor
- Cervical Cancer

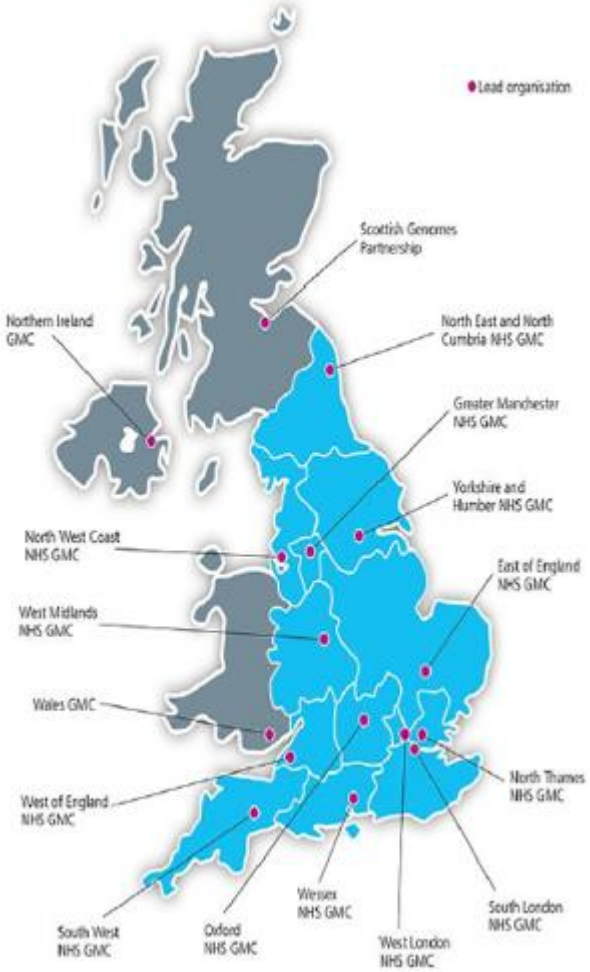
As expected, NSCLC continues to be the most “biomarker-rich” indication

HKBCF x Novartis:
Gene Testing Financial Assistance Program

ACT Genomics	Hong Kong Molecular Pathology Diagnostic Centre	Hong Kong Sanatorium & Hospital	Lucence Diagnostics	Roche	University Pathology Service, CUHK
• ACTDrug® + • ACTMonitor® Breast • ACTOnco® +	• Cancer Hotspot NGS Panel • PIK3CA Hotspot Mutation Test (Blood) • PIK3CA Hotspot Mutation Test (Tissue)	• **PIK3CA by Sanger sequencing** • **PIK3CA by NGS** • Somatic Breast Cancer Panel by NGS	• Liquid HALLMARK • Liquid MARK Breast • **Liquid MARK single PIK3CA gene** • Tissue 500 • Tissue HALLMARK • Tissue MARK Breast • **Tissue MARK single PIK3CA gene**	• FoundationOne CDx • FoundationOne Liquid CDx	• cfDNA PIK3CA test • CUHK Somatic Mutation v3 Test for Solid Cancers (Tissue) • Focused Mutation Panel for solid cancers (Tissue) • PIK3CA gene hotspot mutation detection (Exon 7, 9 and 20) • Roche Avenio surveillance mutation panel for solid cancers on peripheral blood (197 genes) • small RNA fusion panel (15 genes)

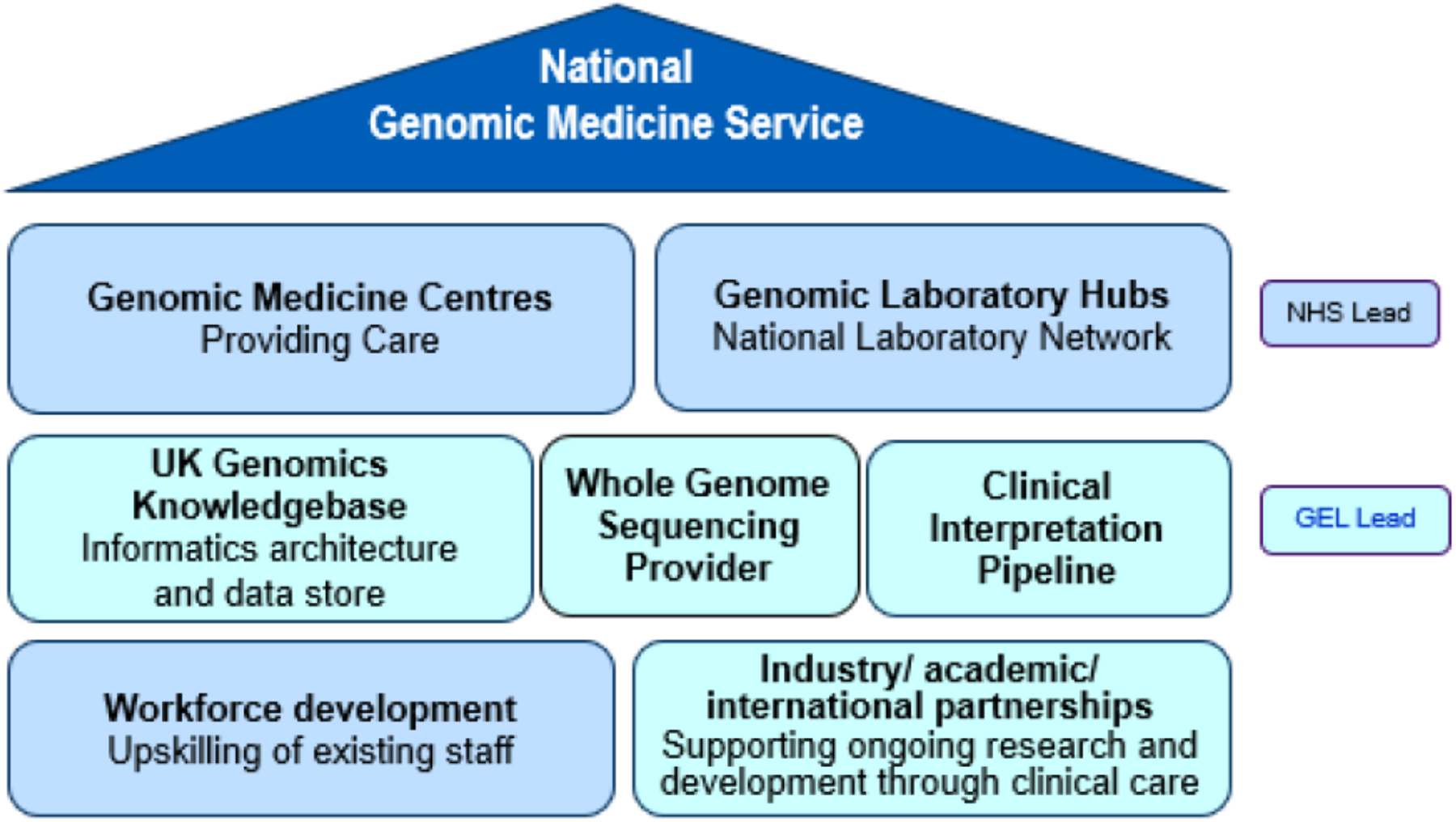
UK 100,000 Genomes Project



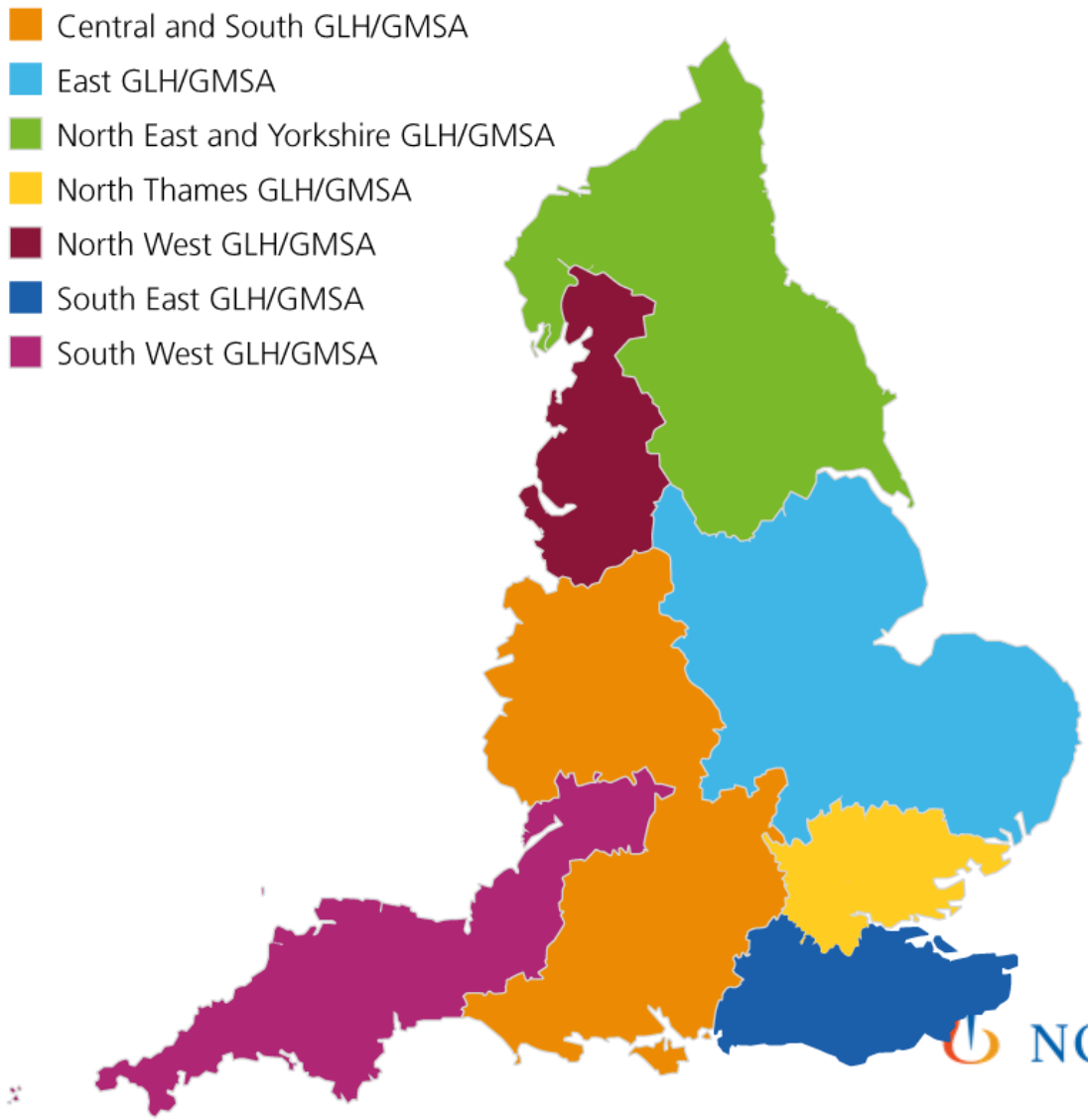


NOVARTIS | Reimagining Medicine

UK Genomic Medicine Service



UK NHS Genomic Medicine Service Regions



Molecular Testing in Cancer

SOLID CANCER REQUEST FORM (31032022) CU-SR-FRM-35 Rev 2 PAGE 1 of 3

SOLID CANCER GENOMIC TEST ORDER FORM

NHS East Genomics

PATIENT DETAILS		REFERENCE INFORMATION	
NHS NO.		SUBMITTER HOSPITAL	
HOSPITAL NO.		CLINICIAN NAME	
SURNAME		DEPARTMENT	
FORENAME		CONTACT EMAIL	Secure NHS.net
ETHNICITY		CONTACT PHONE	
SEX	MALE ☐ FEMALE ☐ OTHER ☐	REQUEST DATE	

SPECIMEN INFORMATION			
SPECIMEN NO		SPECIMEN TYPE	
BLOCK NO.		TISSUE SITE	
DIAGNOSIS		COLLECTION DATE	
REASON FOR REFFERAL			

% TUMOUR CELLS: ☐ CIRCLED ☐ DOTTED ☐ WHOLE SLIDE	☐ <10% ☐ 10-30% ☐ 30-50% ☐ 50-70% ☐ >70

Molecular Testing in Cancer

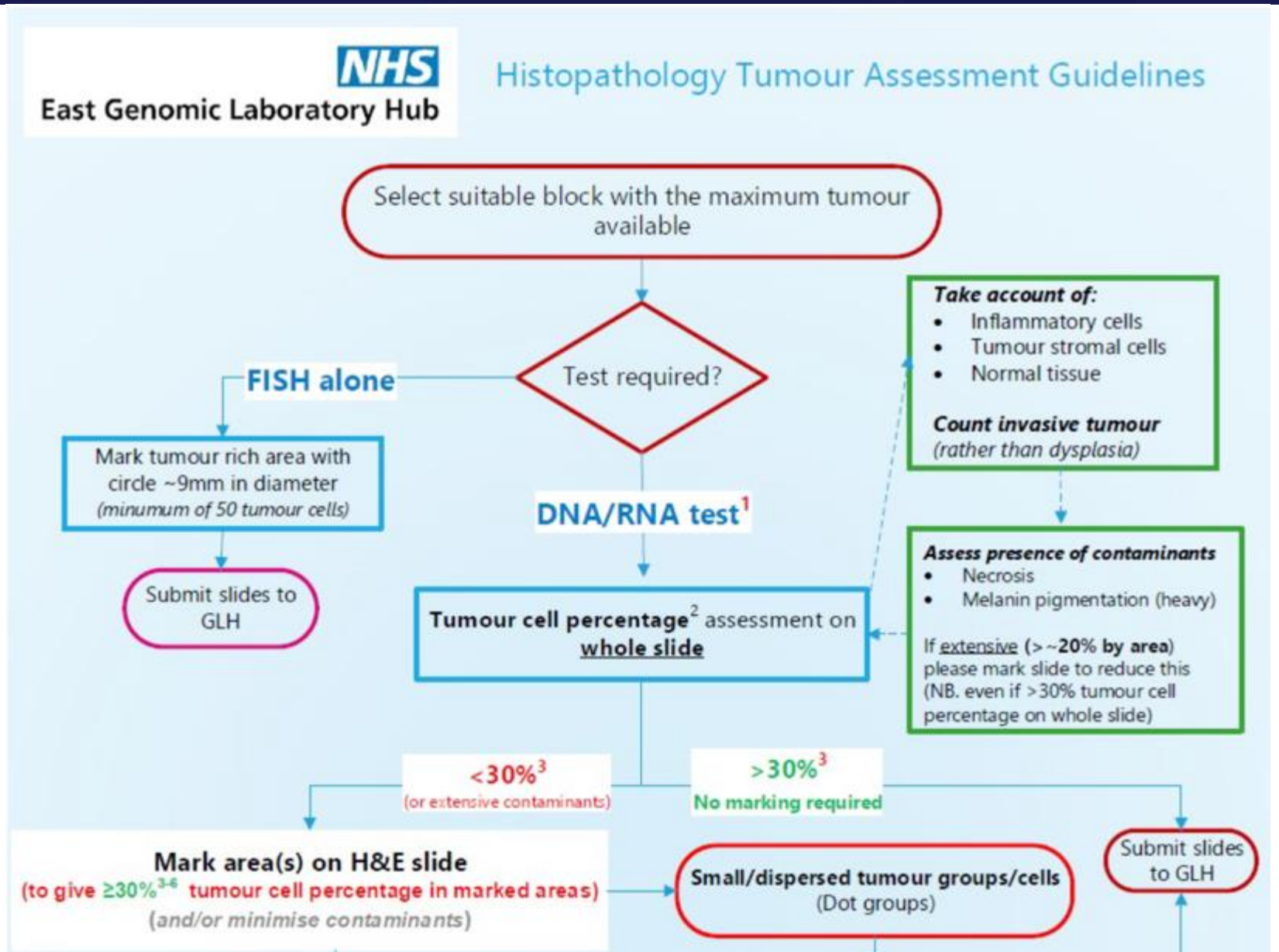
NGS SEQUENCING (tick required box)			
CLINICAL INDICATION	**TEST CODE**	**GENES SCREENED (Bold:** TSO500 large gene panel only)	**ASSAY**
☐ Colorectal Cancer	M1.1	BRAF, KRAS, NRAS, **MLH1**, **MSH2**, **MSH6 PMS2**, **POLE**, **POLD1**	DNA (SNV)
☐ Colorectal Cancer	M1.6	NTRK1/2/3	RNA (FUSION)
☐ Non Small Cell Lung Cancer	M4.1	ALK, BRAF, EGFR, KRAS, MET	DNA (SNV)
☐ Non Small Cell Lung Cancer	M4.2	ALK, ROS1, RET, MET (Ex14 skipping), NTRK1/2/3,	RNA (FUSION)
☐ Melanoma	M7.1	BRAF, KIT, NRAS	DNA (SNV)
☐ Melanoma	M7.3	NTRK1/2/3	RNA (FUSION)
☐ Gastrointestinal Stromal Tumour	M8.1	KIT, PDGFRA, BRAF	DNA (SNV)
☐ Gastrointestinal Stromal Tumour	M8.2	NTRK1/2/3	RNA (FUSION)
☐ Glioma	Specify	IDH1/2, BRAF, CDKN2A, EGFR, TP53, **ATRX, TERT, VHL, YAP1**	DNA (SNV, CNA)
☐ Glioma	Specify	BRAF, MYC, EGFRvIII, NTRK1/2/3	RNA (FUSION)
☐ Thyroid Cancer	Specify	BRAF, KRAS, NRAS, HRAS, RET	DNA (SNV)
☐ Thyroid Cancer	Specify	RET	RNA (FUSION)
☐ Other DNA Indication	Specify	Specify if known	DNA (SNV)
☐ Other RNA Indication	Specify	Specify if known	RNA (FUSION)

Molecular Testing in Cancer

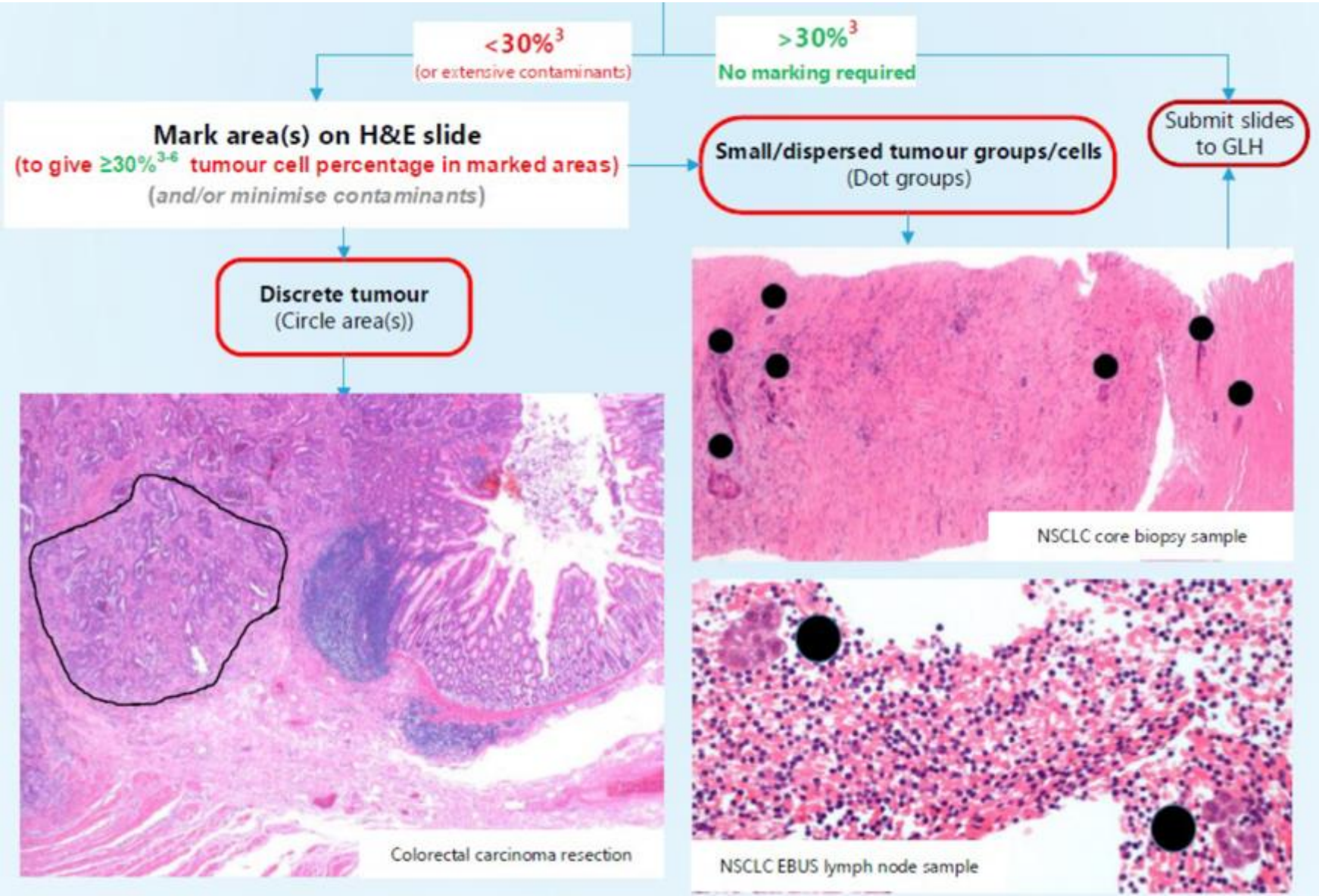
FISH (tick required box)			
CLINICAL INDICATION	**GENES**	**CLINICAL INDICATION**	**GENES**
☐ Neuroblastoma	MYCN, TOP2A, 11q22,3 (ATM), 1p36	☐ Inflammatory Myofibroblastic Tumour	ALK
☐ Ewing's Sarcoma	EWSR1	☐ Angiosarcoma	MYC
☐ Rhabdomyosarcoma	FOX01, PAX3, PAX7	☐ Oligodendroglioma	1p36, 19q13
☐ Dermatofibrosarcoma Protuberans	PDGFB	☐ Medulloblastoma	MYC, MYCN
☐ Synovial Sarcoma	SS18	☐ Gender Identification	CEP X/Y
☐ Infantile Fibrosarcoma	ETV6	☐ Non Small Cell Lung Cancer	ALK, ROS1
☐ Liposarcoma / Osteosarcoma	MDM2	☐ Renal Cell Carcinoma	TFE3
☐ Alveolar Soft Part Sarcoma	TFE3	☐ Mammary Analogue Secretory Carcinoma of Salivary	ETV6

OTHER ASSAYS (tick required box)	
ASSAY	**CLINICAL INDICATION**
☐ Microsatellite Instability	Specify if known
☐ MGMT Promoter Methylation	Specify if known
☐ MLH1 Promoter Methylation	Specify if known
☐ Tissue Identity Testing (STR Genotyping)	Specify if known

Molecular Testing in Breast Cancer



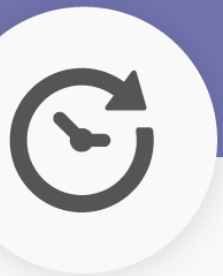
Molecular Testing in Breast Cancer



Molecular Testing in Breast Cancer

Todays Challenges and Barriers for NGS Implementation in a Broader Lab Spectrum

Too slow



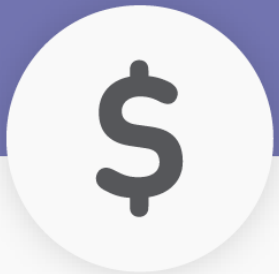
Requires days and often weeks to get the results

Too complex

High level of user expertise required to run NGS

Modular workflows requiring multiple instruments and touchpoints

Too costly



Cost of hiring and training staff

Cost penalty for running small sample batches

Too limited

Tissue requirements / QNS (quantity not sufficient) related failures

Molecular Testing in Breast Cancer

Oncomine Precision Assay on Ion Torrent Genexus System

A new generation solution for genomic profiling

Fast

Single day sample-to-report.

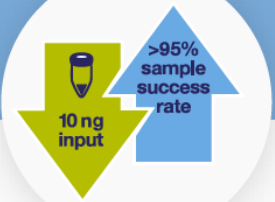
Hands free

2 touch points and only 10 min of hands-on time.

Cost saving

No more need to batch samples across multiple sequencing runs.

Tissue saving



Minimum sample requirement

Maximum results obtained.

Molecular Testing in Breast Cancer

Genexus System—Tomorrow's Specimen-to-Report NGS Workflow

- FFPE tissue
- Frozen tissue
- Bone marrow
- Whole blood
- PBL
- Urine
- Saliva

Genexus Software

Nucleic acid purification and quantitation*	Library preparation to variant interpretation	Report*

Ion Torrent™ Genexus™
Purification System (Available 2020)

2 hour turnaround time
12 FFPE (DNA and RNA)
6 Plasma

Ion Torrent™ Genexus™
Integrated Sequencer (Available November 2019)

Ion Torrent™ GX5™ Chip:
12–15M reads/lane

14 hours for a single-lane run
(approx. 24 to 30 hours for full chip)
Up to 32 Samples per run

Molecular Testing in Breast Cancer

Oncomine Precision Assay Gene Content

DNA hotspots

AKT1	ESR1	MAP2K2
AKT2	FGFR1	MET
AKT3	FGFR2	MTOR
ALK	FGFR3	NRAS
AR	FGFR4	NTRK1
ARAF	FLT3	NTRK2
BRAF	GNA11	NTRK3
CDK4	GNAQ	PDGFRA
CDKN2A	GNAS	PIK3CA
CHEK2	HRAS	PTEN
CTNNB1	IDH1	RAF1
EGFR	IDH2	RET
ERBB2	KIT	ROS1
ERBB3	KRAS	SMO
ERBB4	MAP2K1	TP53

CNV

ALK
AR
CD274
CDKN2A
EGFR
ERBB2
ERBB3
FGFR1
FGFR2
FGFR3
KRAS
MET
PIK3CA
PTEN

Inter-genetic fusions

ALK	**NTRK2**
BRAF	**NTRK3**
ESR1	NUTM1
FGFR1	**RET**
FGFR2	ROS1
FGFR3	RSPO2
MET	RSPO3
NRG1	
NTRK1	

Intra-genetic fusions

AR
BRAF
EGFR
MET

Molecular Testing in Breast Cancer

SOLID CANCER REQUEST FORM V1

Molecular Diagnostics
City Campus
Nottingham University Hospitals
Hucknall Road
Nottingham
NG5 1PB

Genomics and Molecular Medicine
Nottingham University Hospital NHS Trust

SOLID CANCER GENOMIC TEST ORDER FORM

Tel: 0115 969 1169 x77711
E-mail:
nuhnt.molecular.diagnostics@nhs.net
Website:
https://www.nuh.nhs.uk/molecular-diagnostics

PATIENT DETAILS		REFERRER INFORMATION	
SURNAME		REFERRING HOSPITAL	
FORENAME		REFERRER NAME	
DOB		DEPARTMENT	
NHS NO.		CONTACT E-MAIL	
HOSPITAL NO.		CONTACT PHONE	
SEX	☐ MALE ☐ FEMALE ☐ OTHER	REQUEST DATE	

SPECIMEN INFORMATION			
SPECIMEN NO		SPECIMEN TYPE	
BLOCK NO		TISSUE SITE	
DIAGNOSIS		COLLECTION DATE	
TISSUE TYPE	☐ PRIMARY ☐ METASTASIS	☐ BIOPSY ☐ RESECTION ☐ CYTOLOGY	
REFERRAL TYPE	☐ DIAGNOSTIC ☐ TREATMENT-REFLEX ☐ TREATMENT-OTHER		
% TUMOUR CELLS	☐ <20% ☐ 20-30% ☐ 30-50% ☐ 50-70% ☐ >70%		
CELLULARITY	☐ VERY LOW ☐ LOW ☐ INTERMEDIATE ☐ HIGH		

Molecular Testing in Breast Cancer

NGS PANEL TESTING (tick required box)			
CLINICAL INDICATION	TEST CODE[Δ]	GENES SCREENED	ASSAY
☐ Colorectal Cancer	M1.1*	BRAF, KRAS, NRAS	DNA (SNV)
☐ Colorectal Cancer	M1.6	NTRK1/2/3	RNA (FUSION)
☐ Non Small Cell Lung Cancer	M4.1	ALK, BRAF, EGFR, KRAS, MET	DNA (SNV)
☐ Non Small Cell Lung Cancer	M4.2	ALK, ROS1, RET, MET (Ex14 skipping), NTRK1/2/3	RNA (FUSION)
☐ Melanoma	M7.1	BRAF, KIT, NRAS	DNA (SNV)
☐ Melanoma	M7.3	NTRK1/2/3	RNA (FUSION)
☐ Gastrointestinal Stromal Tumour	M8.1	KIT, PDGFRA	DNA (SNV)
☐ Gastrointestinal Stromal Tumour	M8.2	NTRK1/2/3	RNA (FUSION)
☐ Breast Cancer	M3.6	PIK3CA	DNA (SNV)
☐ Breast Cancer	M3.5	NTRK1/2/3	RNA (FUSION)
☐ Glioma	Specify*	IDH1/2, BRAF, CDKN2A, EGFR, TP53	DNA (SNV)
☐ Glioma	Specify*	BRAF, EGFRvIII, NTRK1/2/3	RNA (FUSION)
☐ Thyroid Cancer	Specify*	BRAF, KRAS, NRAS, HRAS, RET, TP53	DNA (SNV)
☐ Thyroid Cancer	Specify*	NTRK1/2/3, RET, ALK	RNA (FUSION)
☐ Other DNA Indication	Specify*	Specify from Genexus OPA Panel	DNA (SNV)
☐ Other RNA Indication	Specify*	Specify from Genexus OPA Panel	RNA (FUSION)

Example NGS Report

Sample Cancer Type: Non-Small Cell Lung Cancer

Relevant Non-Small Cell Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	Not detected	NRAS	Not detected
BRAF	Not detected	NTRK1	Not detected
EGFR	Not detected	NTRK2	Not detected
ERBB2	Not detected	NTRK3	Not detected
KRAS	Not detected	RET	***KIF5B-RET fusion***
MET	Not detected	ROS1	Not detected

Relevant Biomarkers

Tier	Genomic Alteration	Annotations
IA	*KIF5B-RET fusion* kinesin family member 5B - ret proto-oncogene Locus: chr10:32317356 - chr10:43612032	
IIC	*PIK3CA G1049R* phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha Locus: chr3:178952090 Transcript: NM_006218.4	


University of
Nottingham
UK | CHINA | MALAYSIA
Thank You


ThermoFisher
SCIENTIFIC
Oncomine Precision Assay on Ion Torrent Genexus System

HKBCF x Novartis:
Gene Testing Financial Assistance Program

ACT Genomics	Hong Kong Molecular Pathology Diagnostic Centre	Hong Kong Sanatorium & Hospital	Lucence Diagnostics	Roche	University Pathology Service, CUHK
• ACTDrug® + • ACTMonitor® Breast • ACTOnco® +	• Cancer Hotspot NGS Panel • PIK3CA Hotspot Mutation Test (Blood) • PIK3CA Hotspot Mutation Test (Tissue)	• **PIK3CA by Sanger sequencing** • **PIK3CA by NGS** • Somatic Breast Cancer Panel by NGS	• Liquid HALLMARK • Liquid MARK Breast • **Liquid MARK single PIK3CA gene** • Tissue 500 • Tissue HALLMARK • Tissue MARK Breast • **Tissue MARK single PIK3CA gene**	• FoundationOne CDx • FoundationOne Liquid CDx	• cfDNA PIK3CA test • CUHK Somatic Mutation v3 Test for Solid Cancers (Tissue) • Focused Mutation Panel for solid cancers (Tissue) • PIK3CA gene hotspot mutation detection (Exon 7, 9 and 20) • Roche Avenio surveillance mutation panel for solid cancers on peripheral blood (197 genes) • small RNA fusion panel (15 genes)

Overview of the Hong Kong market

Background information and hands on experience

- Before the availability of alpelisib, standard therapies available for HR+/HER2- ABC do not require any molecular or genetic testing prior to treatment, hence precision medicine is not reflexive for most BC clinicians

- Low awareness on the prognostic value of PIK3CA mutation testing for breast cancer patients and how different genetic mutations can impact patient response to available treatments

- PIK3CA mutation testing is readily available through commercially available laboratories and in select government hospital pathology laboratories
  - Clinicians in private sector may opt to choose small or large panel NGS testing for affordable patients, resulting in patients being identified with PIK3CA mutation beyond HR+/HER2- aBC

- Government wide frontline testing using small panel (~52 gene) NGS will be rolled out for lung cancer in 2023 in phases, while plans for this in other solid tumour types are in discussion but pending

Proposed Topics to Discuss

- When and how to test?
- What genes would be important to test in breast cancer moving forward?
  - What genes would you include in a dedicated breast cancer panel?
- Best case sharing and learnings from UK on PIK3CA mutation testing and reimbursement of alpelisib

Proposed Panel Discussion Questions

- Considering the prognostic value of PIK3CA mutation for patients in breast cancer, should we be testing for it upon initial diagnosis rather than just for treatment decision in advanced setting?

- Breast cancer is highly heterogeneous, how can we better characterize the genomic profile or incorporate genetic testing into routine clinical practice for better patient outcomes?

- How can oncologists and pathologists work together to improve patient outcomes?