



Genomics in Cancer Care

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- Genomics
- DNA
- Genome
 - One whole set of your DNA
 - ~3billion nucleotides (A, G, C, T)
 - ~99.9% the same
- Genomic Medicine –utilisation of genomic data to guide diagnosis, predict disease and prognosis and inform therapeutics



- Cancer is a disease of the genome caused by harmful changes in DNA
- Genomic Changes “variants” can be inherited or acquired (germline or somatic)
- May have health implications for the patient

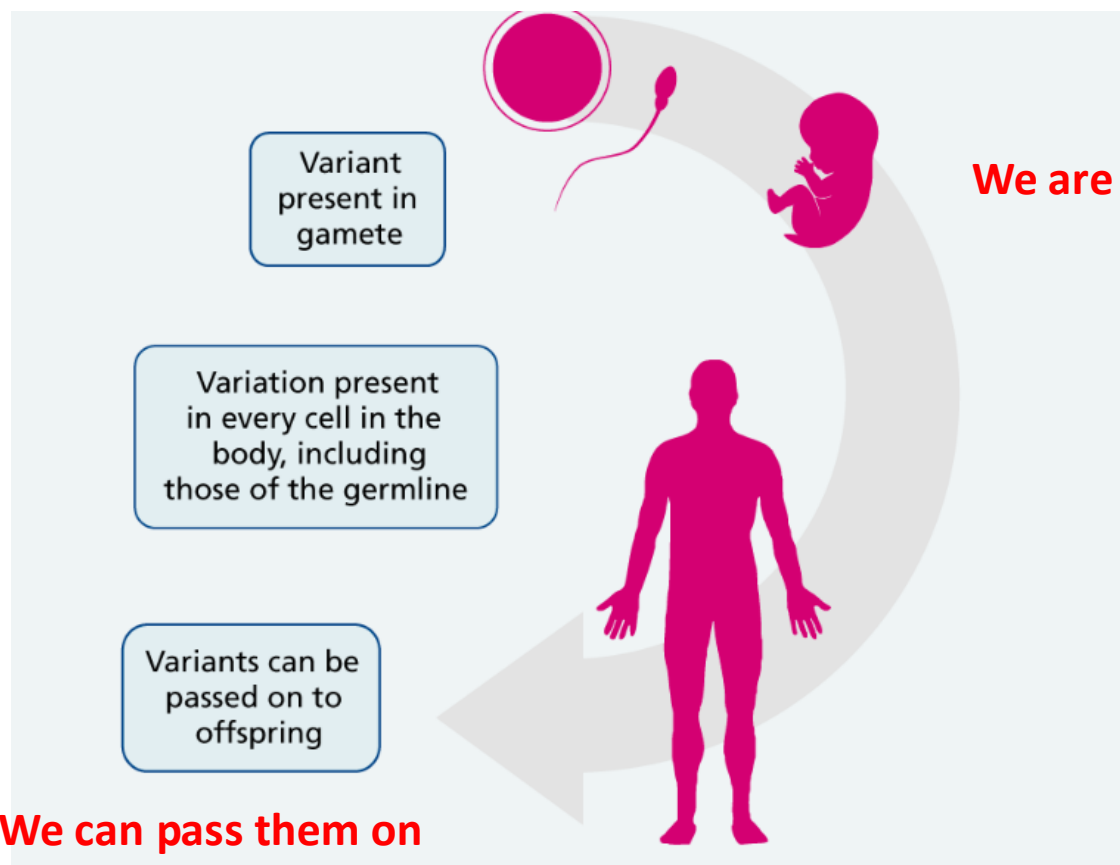


Image shown: Structural Symmetries by Chris Wilson at St. James's Hospital



Inherited (Germline/Constitutional) Variants

Germline Variants

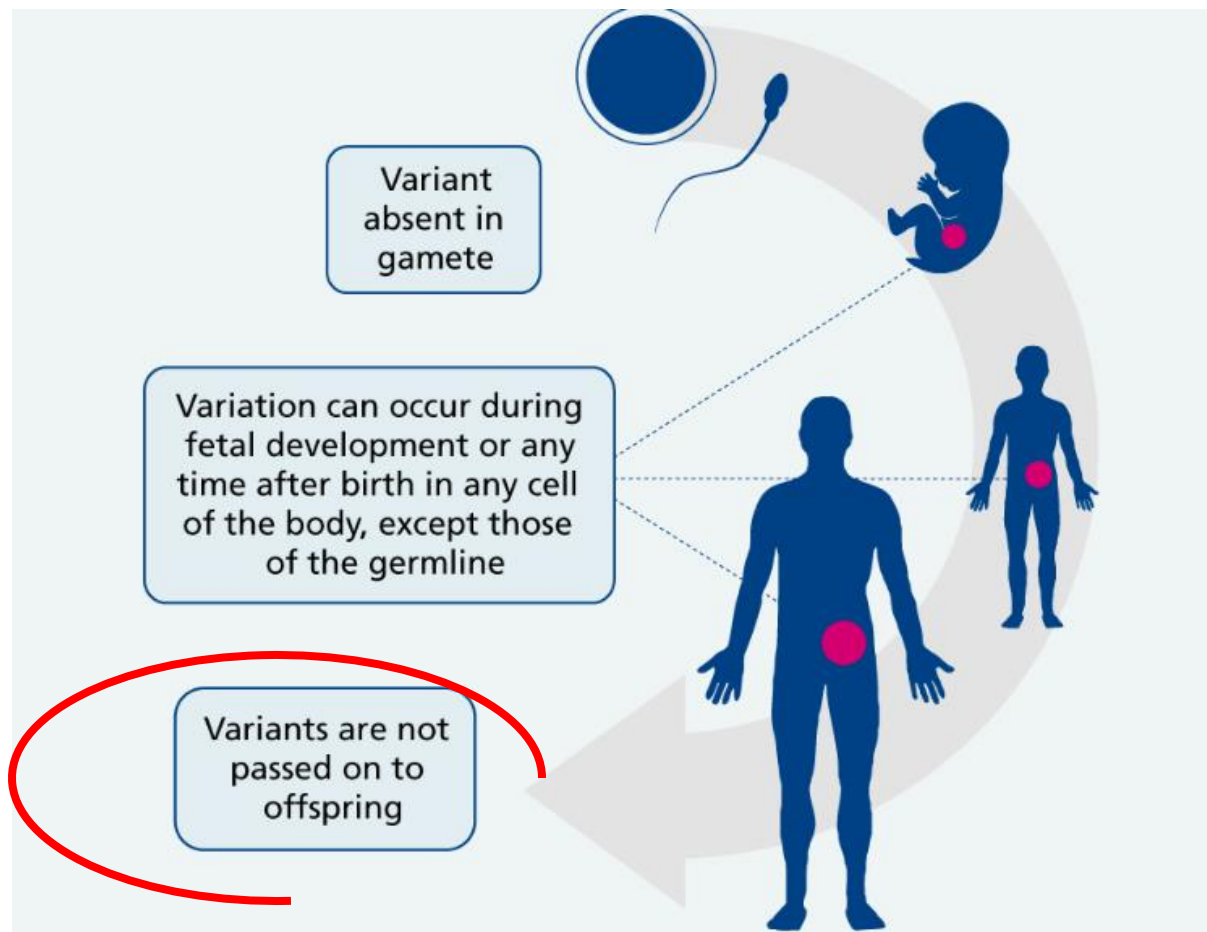


Examples

- Variants predicting risk of conditions e.g. BRCA gene variants in cancer
- Drug Metabolising enzymes and Drug transporter (pharmacogenetics- broader than cancer)

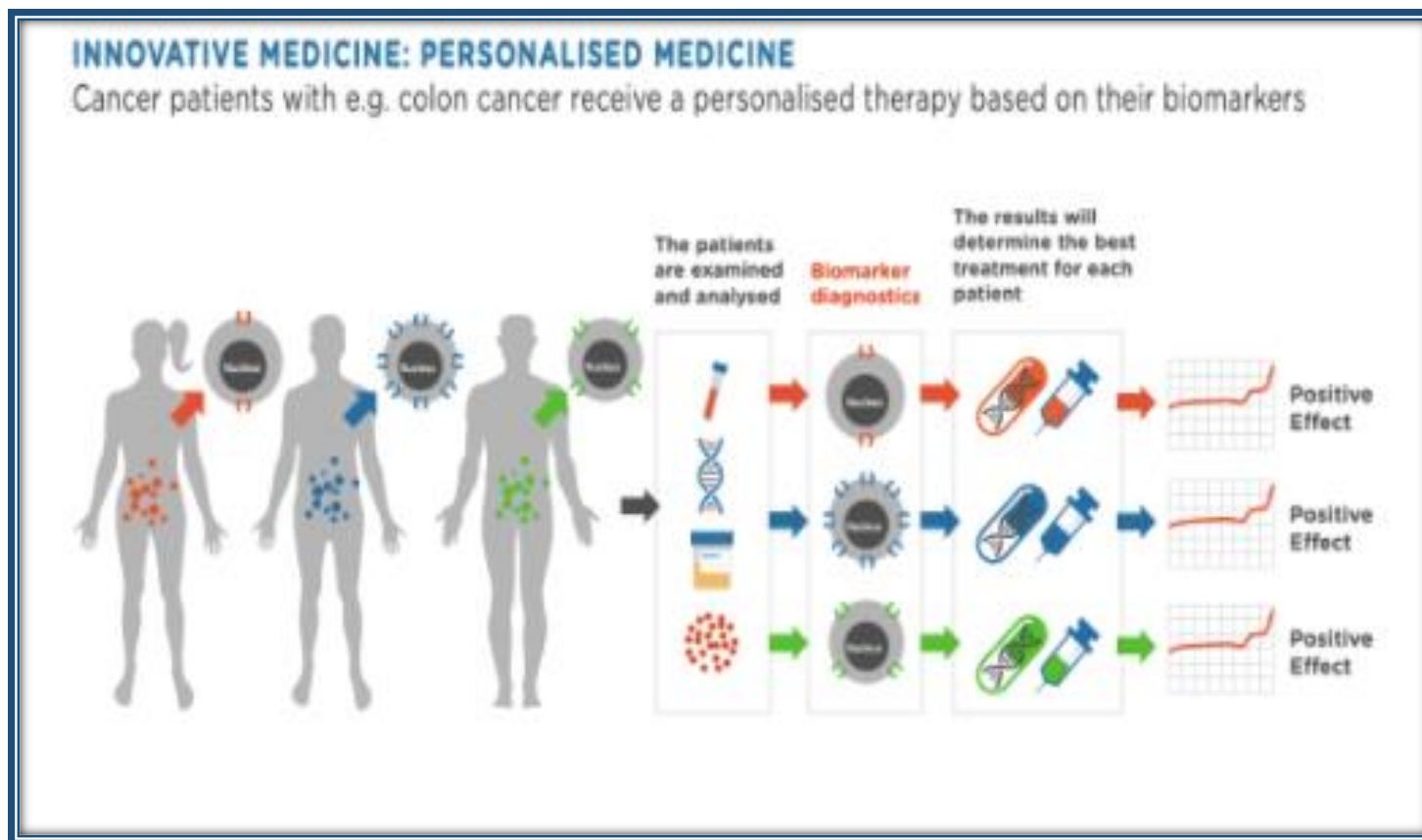


Somatic (Acquired Variant)



- Differ from Inherited variants
 - Happen over our lifetime
 - **Not passed onto future generations**

- **In cancer somatic variants may inform prognosis and treatment selection**





Evolution of Personalised Medicine: HER2 in breast cancer

- Previously treatment was based on tumour type; one size fits all approach
- Chemotherapy affected both healthy cells and cancer cells: bomb like approach
- **1986** : identification of HER2 protein

Human Breast Cancer: Correlation of Relapse and Survival with Amplification of the HER-2/*neu* Oncogene

DENNIS J. SLAMON, GARY M. CLARK, STEVEN G. WONG, WENDY J. LEVIN, AXEL ULLRICH, AND WILLIAM L. MCGUIRE [Authors Info & Affiliations](#)

SCIENCE • 9 Jan 1987 • Vol 235, Issue 4785 • pp. 177-182 • DOI: [10.1126/science.3798106](https://doi.org/10.1126/science.3798106)



Evolution of Personalised Medicine: HER2 in breast cancer

- Monoclonal antibody Trastuzumab (Herceptin) developed
 - FDA approved 1998
 - Improvement in clinical outcomes for HER2 positive patients
- Development of other HER2 targeted treatments : pertuzumab, trastuzumab emtansine, trastuzumab deruxtecan





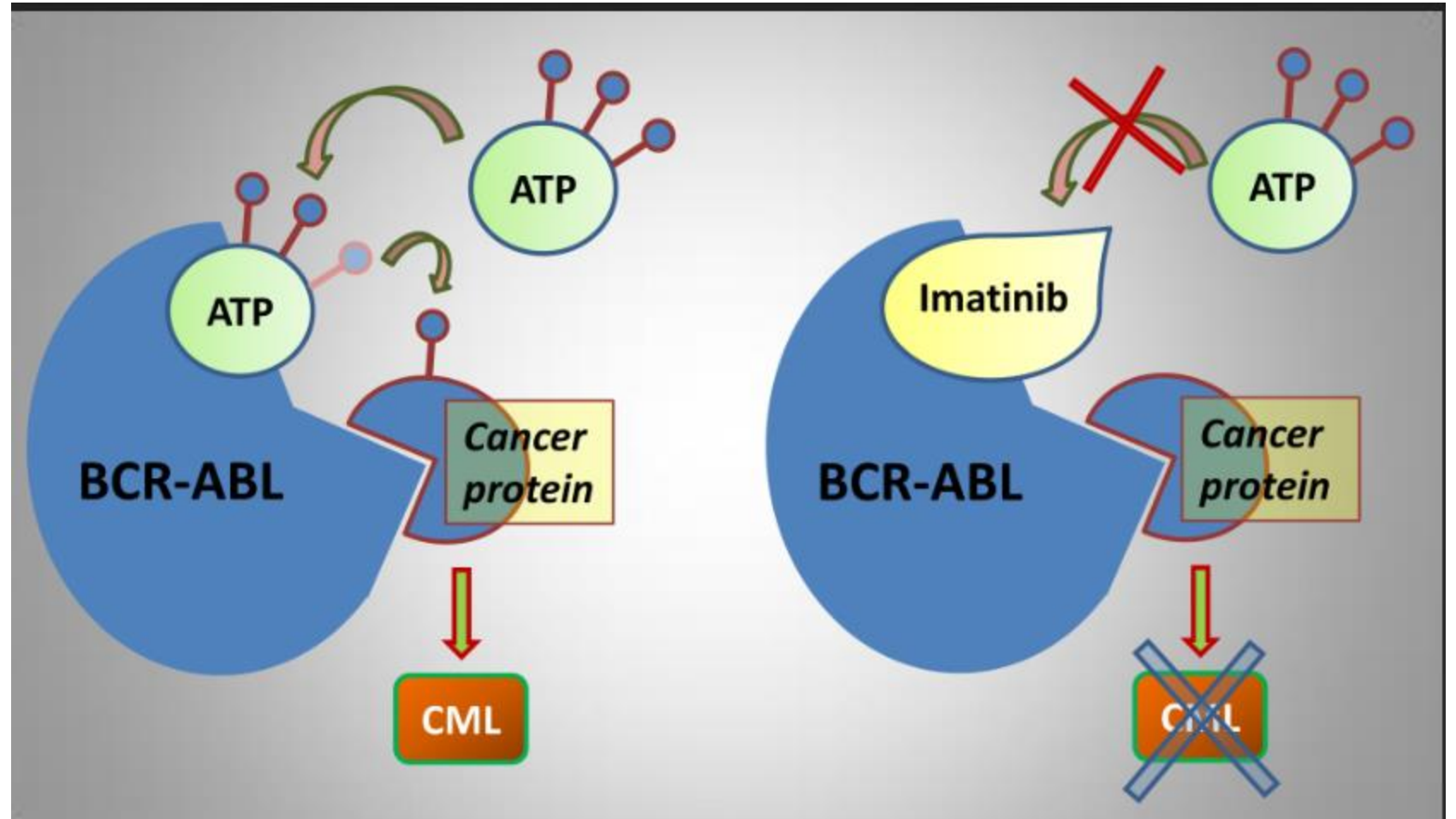
Imatinib in Chronic Myeloid Leukaemia(CML)



- **CML** :abnormal BCR:ABL fusion gene on chromosome 22 (Philadelphia chromosome)

- **Imatinib (Glivec):**

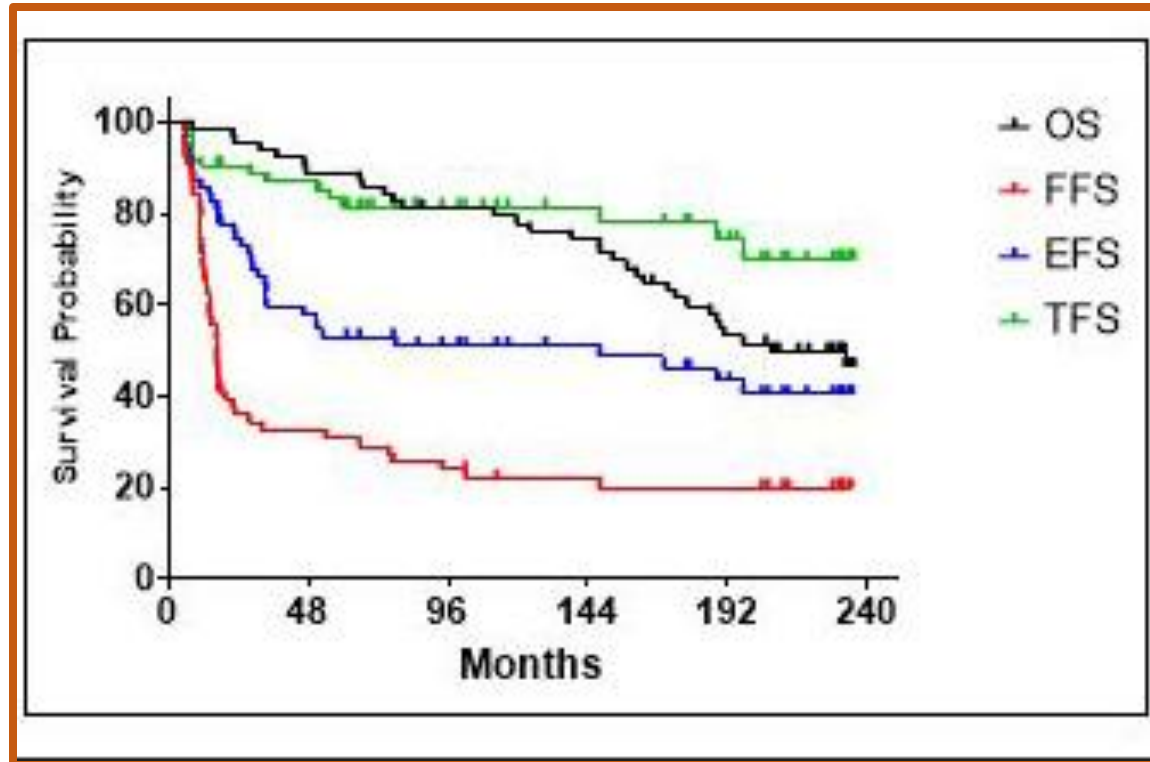
- Specifically targets the ATP binding site of BCR:ABL
- Approved in 2001





Imatinib in Chronic Myeloid Leukaemia

- Reduced progression to acute phase and improves survival
- Transformed CML from a fatal disease to a manageable condition



20 year outcome data

Overall Survival

1yr 98%

5yr 89%

19yr 51%

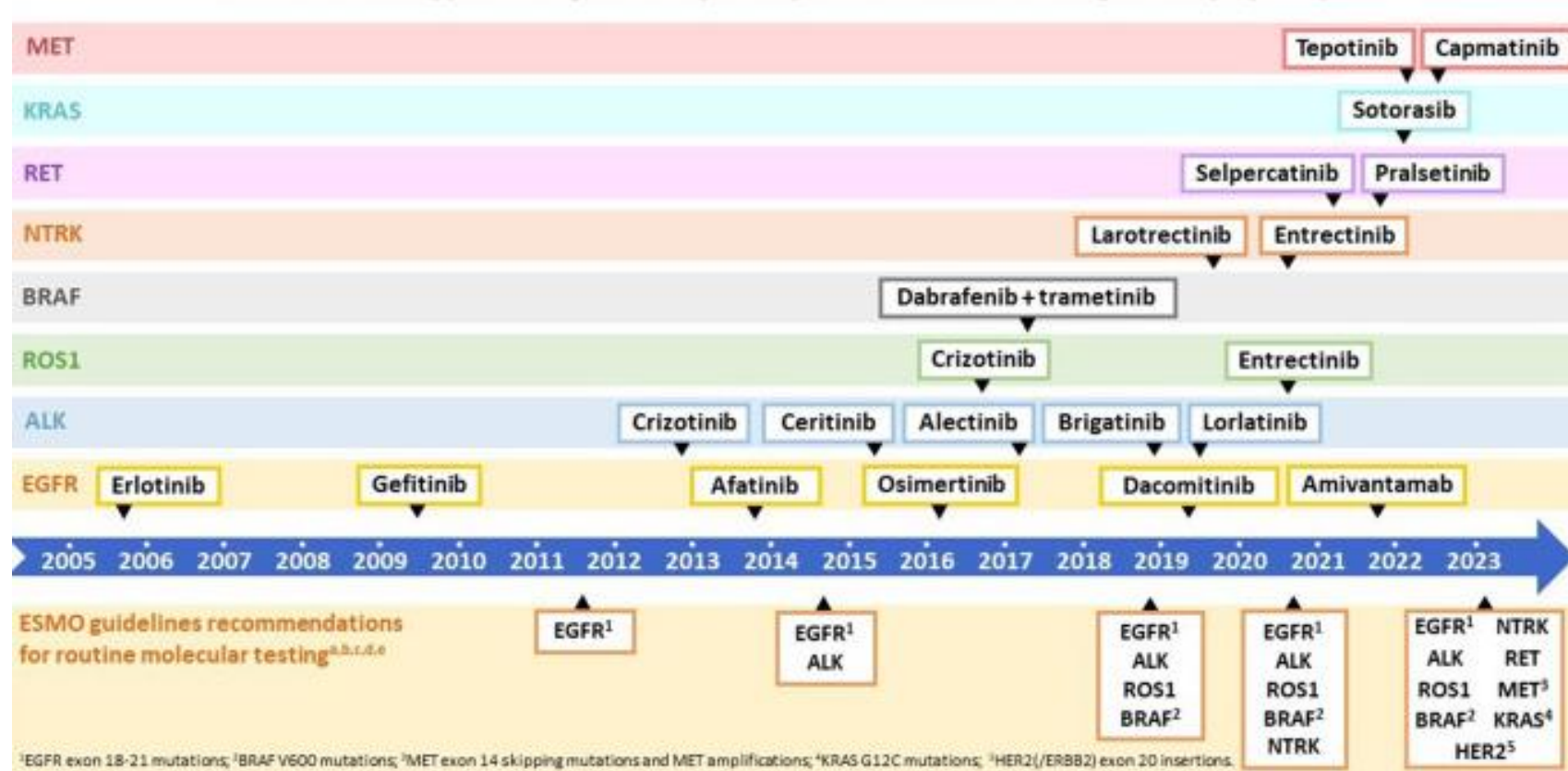
A 20-Year Review of Imatinib in Chronic Phase Chronic Myeloid Leukemia Patients after Failure with Interferon Therapy

Maria R Vazquez, Hagop M. Kantarjian, MD, et al *Blood* (2019) 134 (Supplement_1): 2927.



Advances in Personalised Medicine: Non Small Cell Lung Cancer (NSCLC)

Timeline of EMA-approved targeted therapies for patients with advanced stage NSCLC (July 2023)

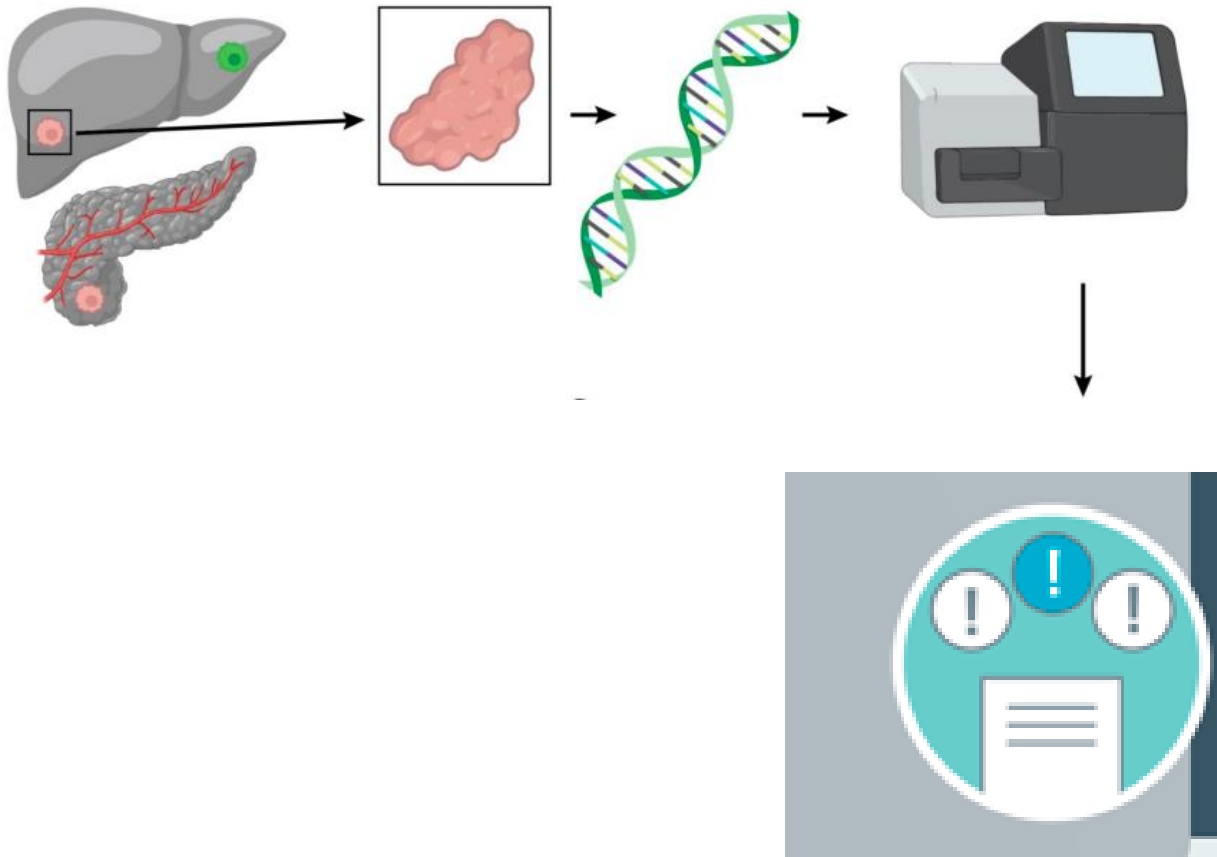


a) Felip E, Grillett C, Baas P, et al. Metastatic non-small-cell lung cancer: consensus on pathology and molecular tests, first-line, second-line, and third-line therapy. 1st ESMO Consensus Conference in Lung Cancer; Lugano 2010. *Ann Oncol.* 2011;22(7):1507-1519.
 b) Kerr KM, Bubendorf L, Edelman MJ, et al. Second ESMO consensus conference on lung cancer: pathology and molecular biomarkers for non-small-cell lung cancer. *Ann Oncol.* 2014;25(9):1681-1690.
 c) Planchard D, Popat S, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up [published correction appears in *Ann Oncol.* 2019 May;30(5):863-870]. *Ann Oncol.* 2018;29(Suppl 4):iv192-iv237.
 d) Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up (2020). <https://www.esmo.org/content/download/347819/6994778/1/ESMO-CPG-mNSCLC-15SEP2020.pdf> (Accessed 20 March 2021).
 e) Hendriks LE, Kerr KM, Menis J, et al. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up [published online ahead of print, 2023 Jan 23]. *Ann Oncol.* 2023;50623-7534(2024)781-0.





Next Generation Sequencing (NGS)

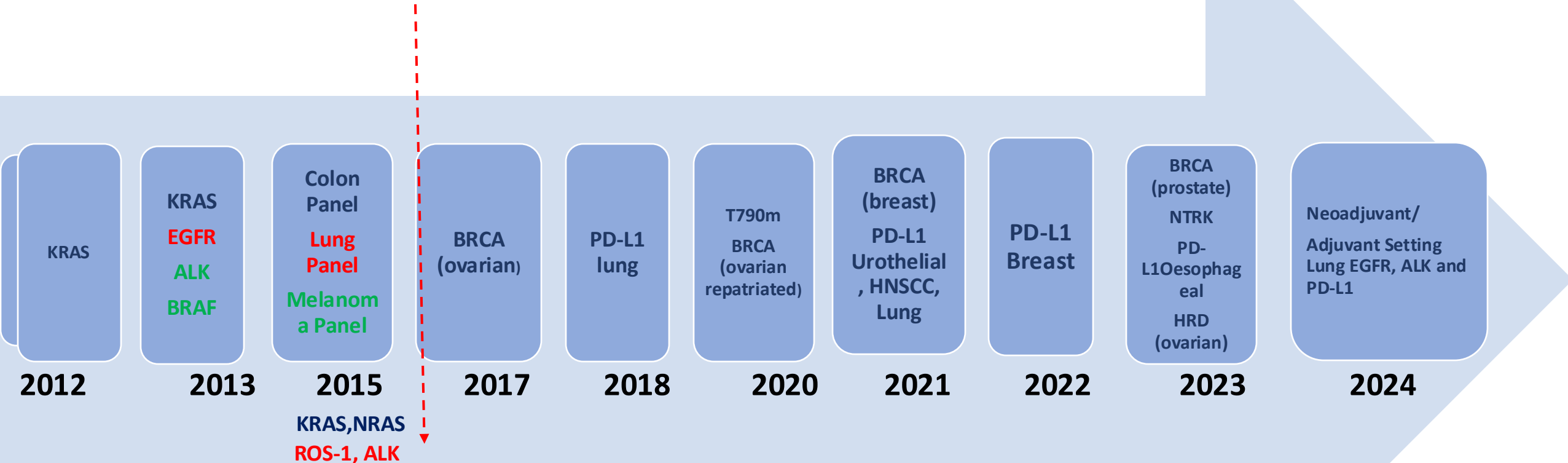


- Used to sequence DNA and RNA
- High throughput massive parallel sequencing technology
- Allows for sequencing of genes (gene panels < 50, up to 500 genes or whole genome in a short period)



Somatic genomic Testing-New testing pathways

NCCP Molecular Diagnostics Advisory Group





NCCP Genomic Test Directory for Cancer

- Scope: Somatic Genomic tests that are diagnostic, prognostic and predictive for drug use
- Being developed on an iterative process
- Published on NCCP website;
<https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/molecular%20diagnostics%20ag.html>
- Aligns with work of National Genetics and Genomics Office (NGGO)



**National Strategy
for Accelerating
Genetic and Genomic
Medicine in Ireland**



Some examples of Cancer Genomic Testing in practice



Patient requiring Capecitabine Therapy

EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine

30 April 2020

[Press release](#)

[Human](#)

[Pharmacovigilance](#)

[Referrals](#)

EMA has recommended that patients should be tested for the lack of the enzyme dihydropyrimidine dehydrogenase (DPD) before starting cancer treatment with fluorouracil given by injection or infusion (drip) or with the related medicines, capecitabine and tegafur.

As treatment for severe fungal infections with flucytosine (another medicine related to fluorouracil) should not be delayed, testing patients for DPD deficiency before they start treatment is not required

- **Dihydropyrimidine dehydrogenase (DPD) encoded by DPYD gene**
 - **Example of Germline (Constitutional) variant**
- **Responsible for breakdown of fluoropyrimidines**
- **Risk of severe toxicity**



Patient requiring Capecitabine Therapy

NCCP Chemotherapy Regimen



Capecitabine Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimburs Status
Treatment of patients with locally advanced or metastatic breast cancer	C50	00216a	CDS
Treatment of metastatic colorectal cancer	C18	00216b	CDS
Adjuvant treatment of patients following surgery of stage III colon cancer	C18	00216c	CDS
Adjuvant treatment of patients following surgery of stage II colon cancer ¹	C18	00216d	CDS
Adjuvant treatment of patients with metastatic colorectal cancer following complete resection ¹	C18	00216e	CDS
Adjuvant treatment of stage I to IIIB, triple negative breast cancer (TNBC) in patients with residual invasive disease after neoadjuvant chemotherapy treatment ¹	C50	00216f	CDS

EXCLUSIONS:

- Hypersensitivity to capecitabine or any of the excipients
- Known complete DPD deficiency
- History of severe and unexpected reactions to fluoropyrimidine therapy
- Pregnancy and lactation
- Severe hepatic or renal impairment
- Recent or concomitant treatment with brivudine

PRESCRIPTIVE AUTHORITY:

- The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- DPD testing prior to first treatment with capecitabine using phenotype and/or genotype testing unless patient has been previously tested

Regular tests:

- FBC, renal and liver profile prior to each cycle.

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Consider a reduced starting dose in patients with identified partial DPD deficiency
 - Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring
- Any dose modification should be discussed with a Consultant





PARP Inhibitors

- **BRCA status : Inherited v somatic**

Tumour	Drug	BRCA status
Breast	Talazoparib (Talzenna™)	Germline BRCA
Prostate	Olaparib (Lynparza™) Niraparib and Abiraterone (Akeega™)	May have a somatic or germline BRCA or both
Ovarian	Olaparib (Lynparza™)	Depends on indication

- Patient Information Leaflet available on NCCP website

<https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/sactguidance/testing-to-inform-parp-inhibitor-cancer-treatment-patient-information-leaflet.pdf>



Testing to inform
PARP inhibitor
cancer treatment
Patient Information Leaflet

Note: There is information on a number of tests in this leaflet. You may only need one test or a combination of tests depending on your cancer.

Case Study : Somatic Testing : advanced Non Small Cell Lung Cancer (NSCLC)

Mr Smith

Diagnosis : advanced adenocarcinoma NSCLC

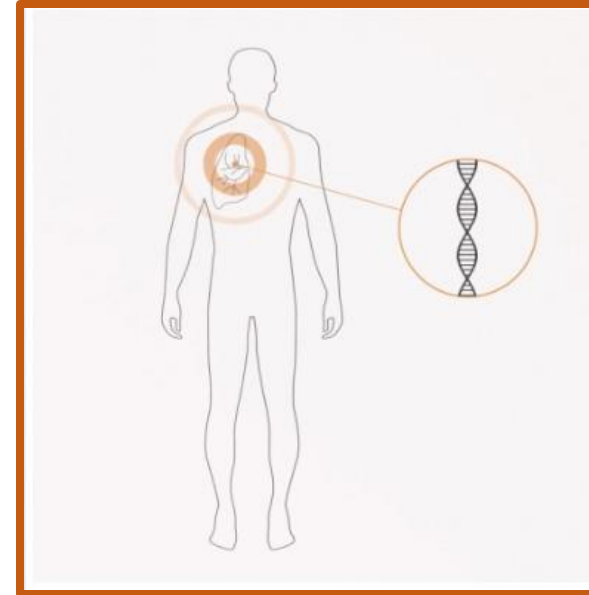
Somatic Genomic Testing to inform treatment options

1. NGS panel for the following biomarkers :

EGFR, ALK, BRAF, MET, ROS 1, KRAS, NTRK1, NTRK2, NTRK3

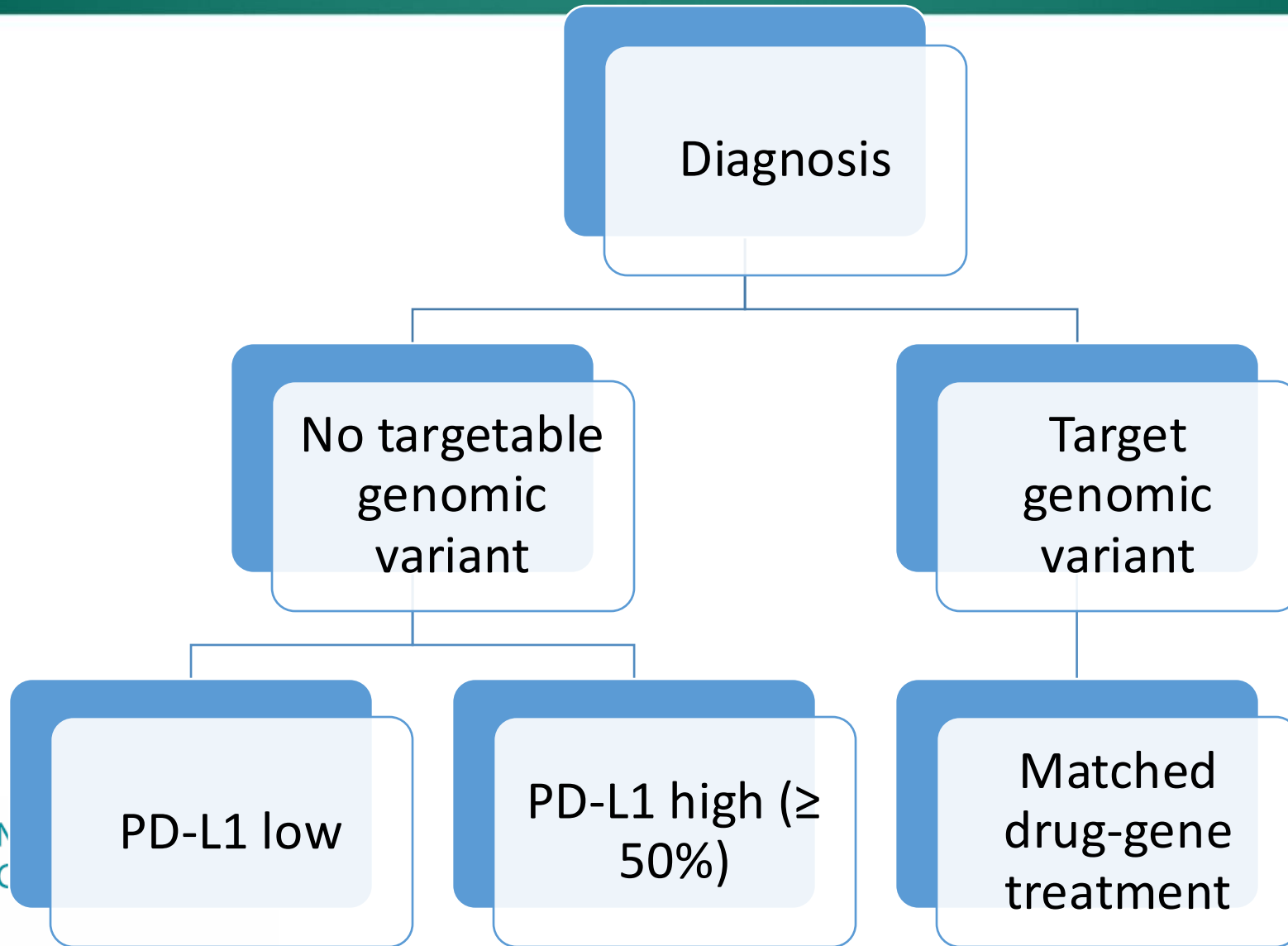
2. PD-L1 testing

- Used to inform immunotherapy treatment options (administered in hospital setting)
 - Immunohistochemistry test- looking at protein expression



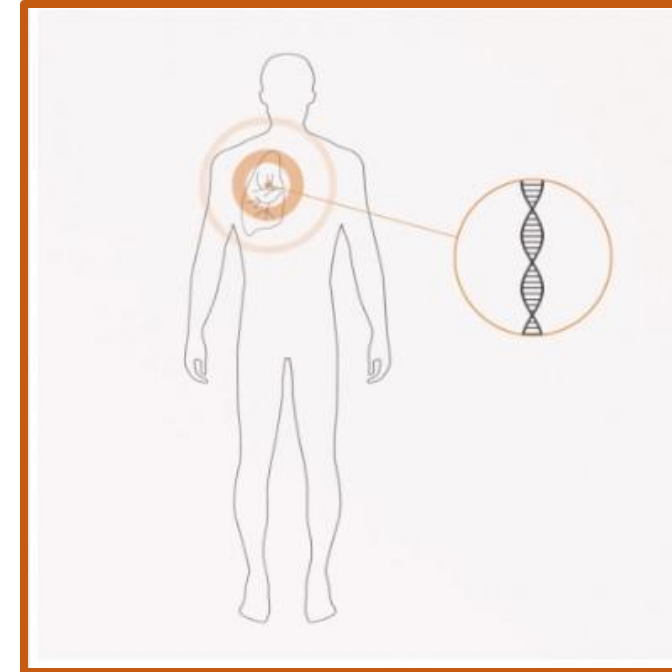


Case Study : Somatic Testing : metastatic Non Small Cell Lung Cancer (NSCLC)



Case Study : Somatic Testing : metastatic Non Small Cell Lung Cancer

Biomarker	Drug
EGFR variants	afatinib, dacomitinib, erlotinib, gefitinib, osimertinib
ALK fusion genes	alectinib, brigatinib, ceritinib
ROS-1 fusion genes	crizotinib, entrectinib
MET exon 14 skipping variants	tepotinib
NTRK1,NTRK2,NTRK3	entrectinib, larotrectinib (when all other treatment options have been exhausted) Managed Access Protocol in place



Patients with EGFR mutations do not benefit from immunotherapy



Breast Cancer : Oncotype DX™ testing

- Gene expression profiling test
- Used for specific cohorts of early stage invasive breast cancer patients
- **Prognostic and Predictive**
 - Determines likelihood of cancer recurring
 - Potential benefit of chemotherapy to a patient after surgery

Breast Cancer Research and Treatment (2021) 188:789–798
<https://doi.org/10.1007/s10549-021-06211-w>

EPIDEMIOLOGY



Real-world analysis of clinical and economic impact of 21-gene recurrence score (RS) testing in early-stage breast cancer (ESBC) in Ireland

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- Liquid biopsy: circulating tumour DNA (ctDNA)
 - Early detection (NHS Galleri trial)
 - Monitoring treatment
 - Checking for recurrence after treatment has finished
 - Identify somatic variants to inform treatment options
- Molecular Tumour Boards





Cancer and Somatic Genomic Testing-Future

