Cancer Genetics and Genomics for the GP

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Annual GP Study Morning

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THIS IS MODERN MEDICINE

Cancer Genetics and Genomics

- What are cancer genetics and genomics?
- How they affect practice?
- Relevance to GP practice…

Cancer Genetics

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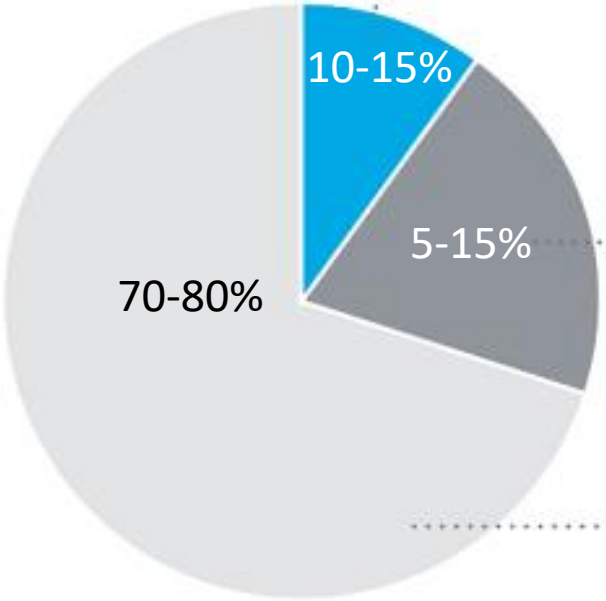
Types of Cancer



HEREDITARY CANCER

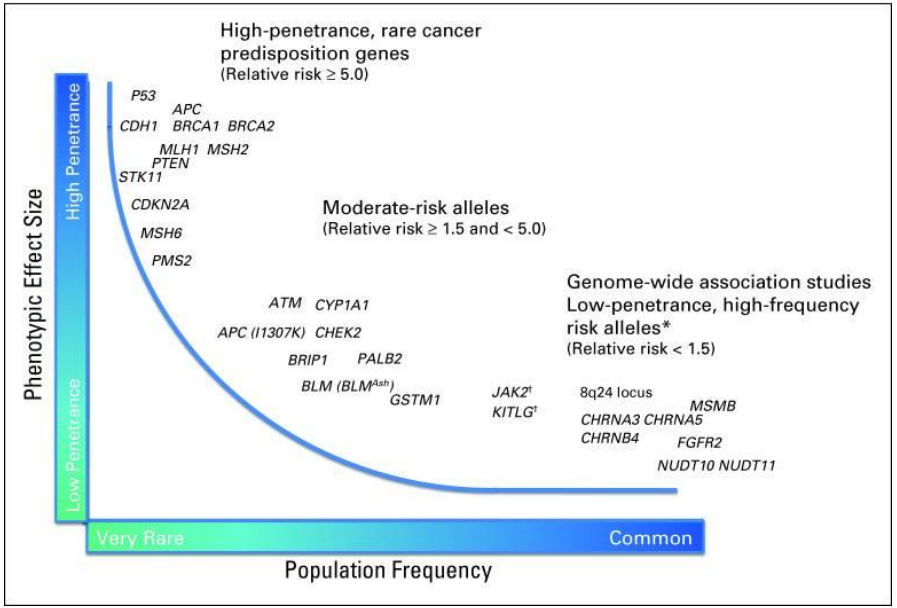
A clustering of cancer in a family due to inherited gene changes (mutations), which can be passed from parent to child

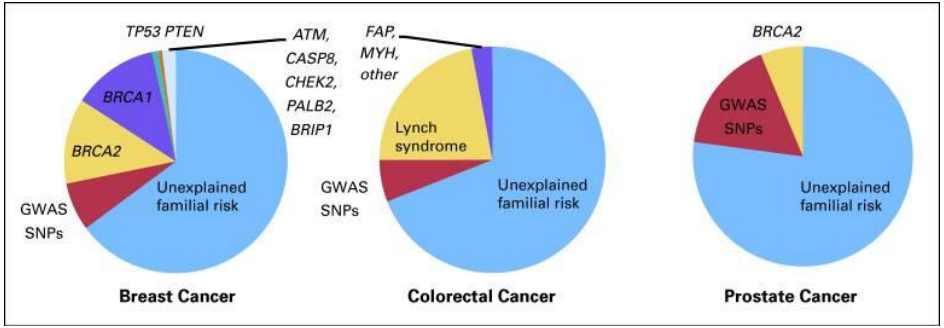
FAMILIAL CANCER

A clustering of cancer in a family that may be due to genes and/or other shared factors, such as environment and lifestyle

SPORADIC CANCER

Happens by chance in one or two related family members, typically at older ages





Stadler et al. JCO 2010

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Who should be tested? International guidelines

TESTING CRITERIA FOR HIGH-PENETRANCE BREAST AND/OR OVARIAN CANCER SUSCEPTIBILITY GENES
(This can include *BRCA1, BRCA2, CDH1, PALB2, PTEN,* and *TP53*

- **Breast cancer <u>AND</u>**
  - Dx <45 yrs
  - Dx 46-50 yrs with unknown FHx, 2nd breast ca dx at any age, >=1 close relative with breast, ovarian, pancreatic, prostate ca (any age)
  - TNBC < 60 yrs
  - Any male breast cancer
  - Dx at any age <u>with</u>
    - >= 1 close relative with breast ca at <50yrs or ovarian, pancreatic, met/high risk prostate ca at any age
    - Ashkenazi Jewish ancestry

Who should be tested?

- **Ovarian cancer** at any age
- **Exocrine pancreatic cancer** at any age
- **Prostate cancer** at any age **AND** metastatic/high risk group
- Meets **Li-Fraumeni** or **Cowden** syndrome criteria
- Any unaffected individual with a relative who has a known cancer susceptibility gene or with a 1st or 2nd degree relative meeting any of the criteria above
- Any individual who meets criteria above but tested negative with previous limited testing

Who should be tested?

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021 Hereditary Cancer Testing Criteria

TESTING CRITERIA FOR LI-FRAUMENI SYNDROME[a]

- Individual from a family with a known *TP53* pathogenic/likely pathogenic variant
- Classic Li-Fraumeni syndrome (LFS) criteria:[p]
  - Combination of an individual diagnosed at age <45 years with a sarcoma[q]
    AND
    A first-degree relative diagnosed at age <45 years with cancer
    AND
    An additional first- or second-degree relative in the same lineage with cancer diagnosed at age <45 years, or a sarcoma at any age
- Chompret criteria:[r,s]
  - Individual with a tumor from LFS tumor spectrum (eg, soft tissue sarcoma, osteosarcoma, CNS tumor, breast cancer, adrenocortical carcinoma), before 46 years of age, AND at least one first- or second-degree relative with any of the aforementioned cancers (other than breast cancer if the proband has breast cancer) before the age of 56 years or with multiple primaries at any age
    OR
  - Individual with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum with the initial cancer occurring before the age of 46 years
    OR
  - Individual with adrenocortical carcinoma, or choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype, at any age of onset, regardless of family history
    OR
  - Breast cancer before 31 years of age
- Affected individual with pathogenic/likely pathogenic variant identified on tumor genomic testing that may have implications if also identified on germline testing[t]

TESTING CRITERIA FOR COWDEN SYNDROME (CS)/PTEN HAMARTOMA TUMOR SYNDROME (PHTS)[a,u,v,w]

- Individual from a family with a known *PTEN* pathogenic/likely pathogenic variant
- Individual with a personal history of Bannayan-Riley-Ruvalcaba syndrome (BRRS)
- Individual meeting clinical diagnostic criteria[x] for CS/PHTS
- Individual not meeting clinical diagnostic criteria[x] for CS/PHTS with a personal history of:
  - Adult Lhermitte-Duclos disease (cerebellar tumors); or
  - Autism spectrum disorder and macrocephaly; or
  - Two or more biopsy-proven trichilemmomas; or
  - Two or more major criteria (one must be macrocephaly); or
  - Three major criteria, without macrocephaly; or
  - One major and ≥3 minor criteria;[y] or
  - ≥4 minor criteria
- At-risk individual with a relative with a clinical diagnosis of CS/PHTS or BRRS for whom testing has not been performed
  - The at-risk individual must have the following:
    - Any one major criterion or
    - Two minor criteria
- *PTEN* pathogenic/likely pathogenic variant detected by tumor profiling on any tumor type in the absence of germline analysis[z]

FOLLOW-UP

- CS/PHTS testing criteria met → See GENE-1
- If CS/PHTS testing criteria not met, consider testing for other hereditary syndromes, if appropriate → Individualized recommendations according to personal and family history

Major criteria:

- Breast cancer
- Endometrial cancer
- Follicular thyroid cancer
- Multiple GI hamartomas or ganglioneuromas[aa]
- Macrocephaly (megalocephaly) (ie, ≥97%, 58 cm in adult women, 60 cm in adult men)[bb]
- Macular pigmentation of glans penis
- Mucocutaneous lesions[cc]
  - One biopsy-proven trichilemmoma
  - Multiple palmoplantar keratoses
  - Multifocal or extensive oral mucosal papillomatosis
  - Multiple cutaneous facial papules (often verrucous)

Minor criteria:[dd]

- Autism spectrum disorder
- Colon cancer
- ≥3 esophageal glycogenic acanthoses
- Lipomas
- Intellectual disability (ie, IQ ≤75)
- Papillary or follicular variant of papillary thyroid cancer
- Thyroid structural lesions (eg, adenoma, nodule[s], goiter)
- Renal cell carcinoma
- Single GI hamartoma or ganglioneuroma
- Testicular lipomatosis
- Vascular anomalies (including multiple intracranial developmental venous anomalies)

[a] For further details regarding the nuances of genetic counseling and testing,

[y] If an individual has two or more major criteria, such as breast cancer and non-medullary thyroid cancer, but does not have macrocephaly, one of the major criteria may be included as one of the three minor criteria to meet testing criteria.

[z] This should prompt a careful evaluation of personal and family history of the individual to determine the yield of germline sequencing. Somatic PTEN pathogenic/likely pathogenic variants are common in many tumor types in absence of germline pathogenic/likely pathogenic variant.

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Who should be tested?

CRITERIA FOR THE EVALUATION OF LYNCH SYNDROME

- **Known LS pathogenic variant in the family**
- **Personal history of a tumor with MMR deficiency determined by PCR, NGS, or IHC diagnosed at any age[a] (See LS-A)**
- **An individual with colorectal or endometrial cancer and any of the following:**
  - **Diagnosed <50 y**
  - **A synchronous or metachronous LS-related cancer[b]**
  - **1 first-degree or second-degree relative with an LS-related cancer[b] diagnosed <50 y**
  - **≥2 first-degree or second-degree relatives with an LS-related cancer[b] regardless of age**
- **Family history[c] of any of the following:**
  - **≥1 first-degree relative with a colorectal or endometrial cancer diagnosed <50 y**
  - **≥1 first-degree relative with a colorectal or endometrial cancer and a synchronous or metachronous LS-related cancer[b]**
  - **≥2 first-degree or second-degree relatives with LS-related cancers,[b] including ≥1 diagnosed <50 y**
  - **≥3 first-degree or second-degree relatives with LS-related cancers,[b] regardless of age**

Indications:
- ≥10 colorectal adenomas
- First degree relative with clinical diagnosis of FAP/AFAP or germline APC pathogenic variant

↓

Genetic counseling process:
- Family history evaluation
- Education
- Review implications and management recommendations
- Informed consent for genetic testing

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National Cancer Control Programme

Criteria for diagnostic BRCA1/2 testing:

Affected individual with:	*Comments:*
• Breast cancer (or ovarian, pancreatic, prostate or male breast cancer,) who has relatives with cancer and a Manchester Score ≥ 15. (on same side of family)	Using pathology adjusted Manchester scoring system (MSS3), J Med Genet. 2017 Oct;54(10):674-681 Evans
• Breast cancer dx < 30 years	If nil found on BRCA1/2 testing, then TP53 testing
• Breast cancer < 40 years, adopted and no available biological FHx	Consider offering testing
• Triple negative breast cancer ≤ 60 years	
• Bilateral/double primary breast cancer and both dx < 50 years, irrespective of family history	J Med Genet. 2010 Aug;47(8):561-6 Evans *et al*
• Ovarian cancer (high grade serous or high grade endometrioid ovarian, fallopian tube or primary peritoneal carcinoma) at any age	
• Male breast cancer who has relatives with cancer and a Manchester Score ≥15	
• Prostate cancer and multiple FDRs (first degree relatives) with prostate cancer (≥3 FDRs or ≥2FDRs and both dx ≤55years)	Cancer. 2018 Aug 1;124(15):3105-3117
• Of Jewish or Polish ancestry AND female breast cancer < 50 years or male breast cancer	Founder BRCA1/2 mutation test ONLY
Unaffected individual:	*Comments:*
• Of Jewish or Polish ancestry who has a FDR with breast cancer <50 years OR a FDR with male breast cancer AND a Manchester score ≥10	AND no living affected family member available for testing, Founder BRCA1/2 mutation screen ONLY

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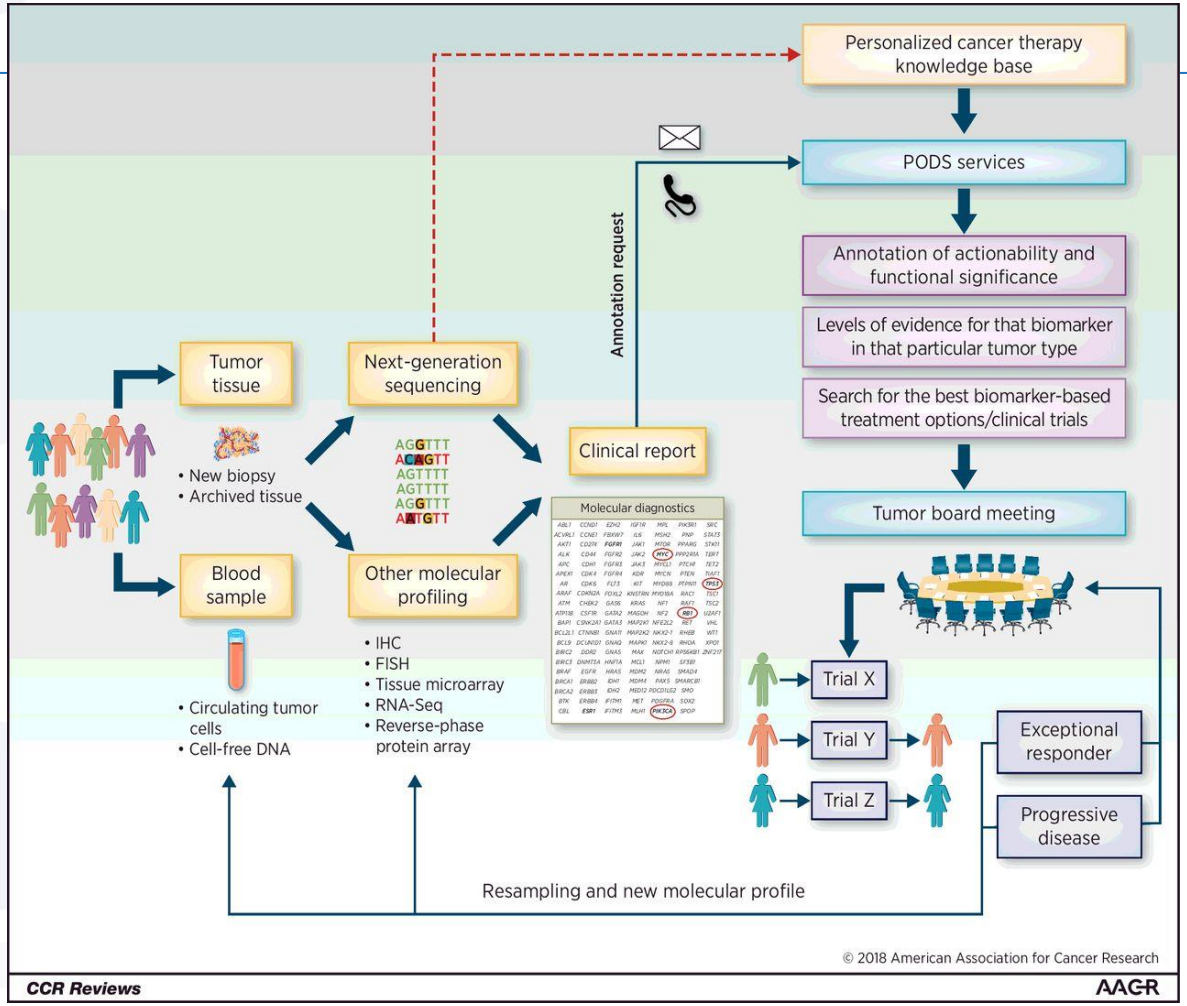
Cancer Genetics Services in Ireland

- St James Hospital
- Our Lady's Children's Hospital, Crumlin

- Mater Private Hospital
- Blackrock clinic
- Hermitage clinic

- Genetic counselling
- Cancer screening
- Risk reduction surgery

Cancer genomics



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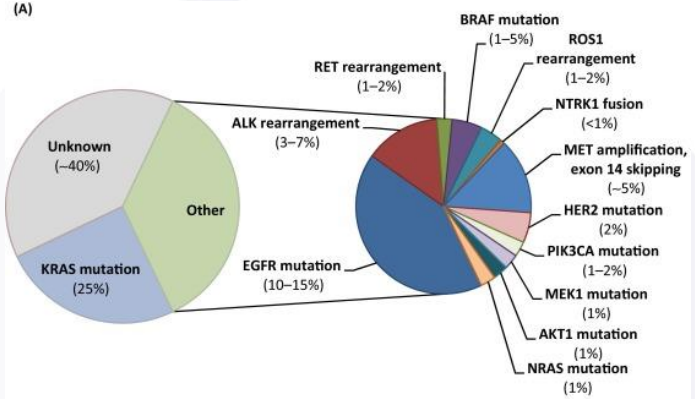
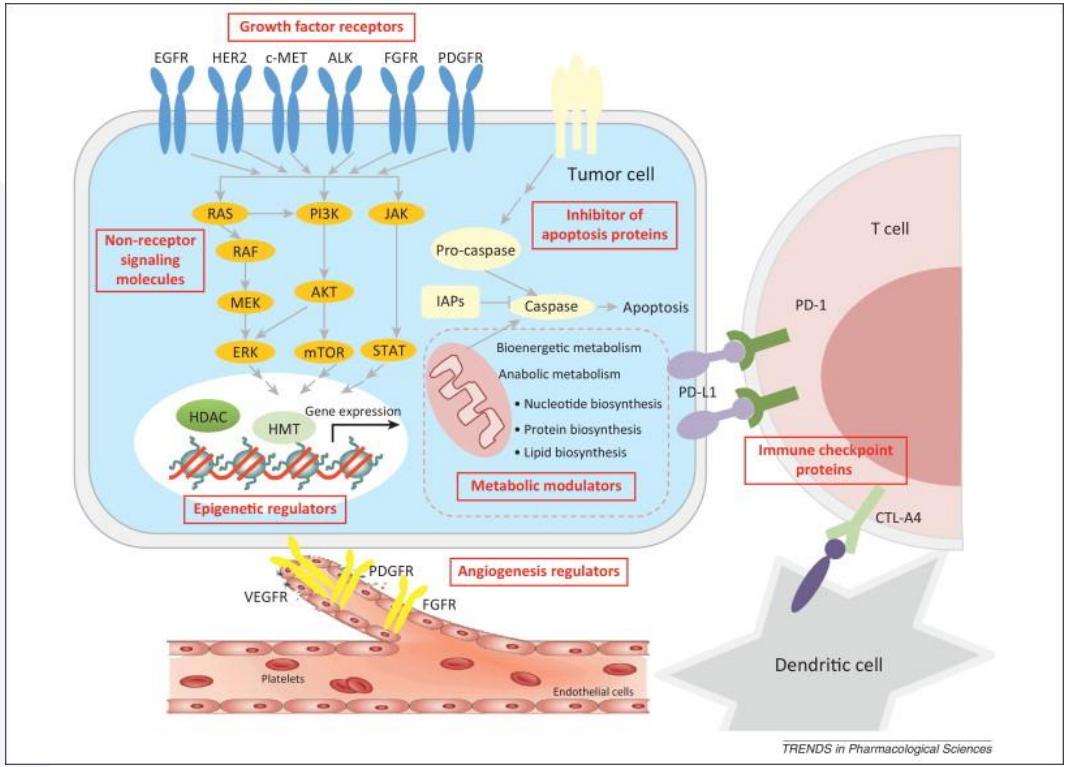
(A)



(B)

Inhibitors			
EGFR	**ALK**	**ROS**	**RET**
Erlotinib* Gefitinib* Afatinib* Osimertinib* Rociletinib EGF816 ASP8273 HM61713	Crizotinib* Ceritinib* Alectinib* Lorlatinib Brigatinib Ensartinib Entrectinib	Crizotinib* Ceritinib Lorlatinib Cabozantinib Foretinib Entrectinib DS-6051b	Alectinib Cabozantinib Vandetanib Lenvatinib Apatinib Ponatinib Sunitinib Dovitinib
MET	**TRK1**	**HER2**	**BRAF/MEK**
Crizotinib Tivantinib Cabozantinib Foretinib Volitinib Capmatinib MSC2156119J AMG337 AMG208	Entrectinib LOXO-101 DS-6051b	Afatinib Dacomitinib Neratinib Lapatinib Pyrotinib	Vemurafenib Dabrafenib Trametinib Selumetinib

Trends in Cancer



Lin. Trends in Cancer. 2016

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FoundationOne Report

FOUNDATIONONE

Patient Name		Report Date		Diagnosis
				Lung adenocarcinoma

Date of Birth	Not Given	Client	Maryland Oncology Hematology	Specimen Received	Not Given
Gender	Female	Physician	Koutrelakos, Nicholas	Specimen Site	Brain
FMI Case #	Not Given	Additional Recipient	Not Given	Specimen Date	Not Given
Medical Record #		FMI Client #	-1	Specimen Type	Block
Block ID	Not Given	Pathologist	Not Given		

ABOUT THE TEST:
FoundationOne™ is a next-generation sequencing (NGS) based assay which identifies genomic alterations within hundreds of cancer-related genes.

PATIENT RESULTS

6 genomic alterations pg - 2
1 therapy associated with potential clinical benefit pg - 3
0 therapies associated with lack of response pg - 3
12 clinical trials pg - 4

TUMOR TYPE: LUNG ADENOCARCINOMA

Genomic Alterations Identified
MET amplification
CCND1 amplification
KRAS G12V
MYC amplification
TP53 R273L
CARD11 N184S

Additional Disease-relevant Genes with No Reportable Alterations Detected
EGFR

THERAPEUTIC IMPLICATIONS

Genomic Alterations Detected	FDA Approved Therapies (in patient's tumor type)	FDA Approved Therapies (in another tumor type)	Potential Clinical Trials
MET amplification	Crizotinib	None	Yes, see clinical trials section
CCND1 amplification	None	None	Yes, see clinical trials section
KRAS G12V	None	None	Yes, see clinical trials section
MYC amplification	None	None	Yes, see clinical trials section
TP53 R273L	None	None	None
CARD11 N184S	None	None	None

Note: Genomic alterations detected may be associated with activity of certain FDA approved drugs; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type.

TUMOR TYPE: LUNG ADENOCARCINOMA

Genomic Alterations Identified
MET amplification
CCND1 amplification
KRAS G12V
MYC amplification
TP53 R273L
CARD11 N184S

Additional Disease-relevant Genes with No Reportable Alterations Detected
EGFR

Crizotinib, METi

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Background

30 year old male

Presented with metastatic BRAF mutated melanoma - Left neck primary melanoma with regional lymphadenopathy, lung and liver metastases

1st line treatment with Pembrolizumab. Received 4 cycles

Restaging CT TAP demonstrated massive progression

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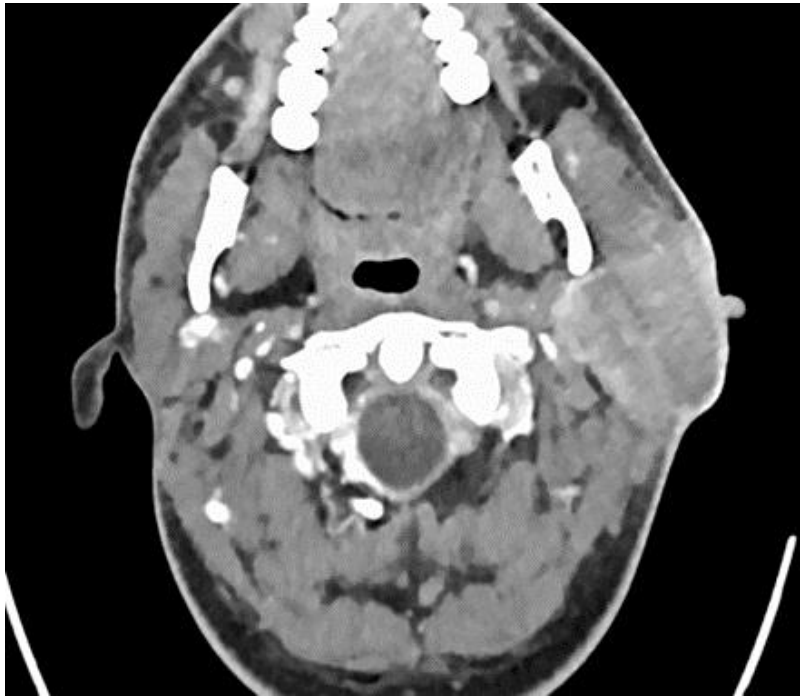
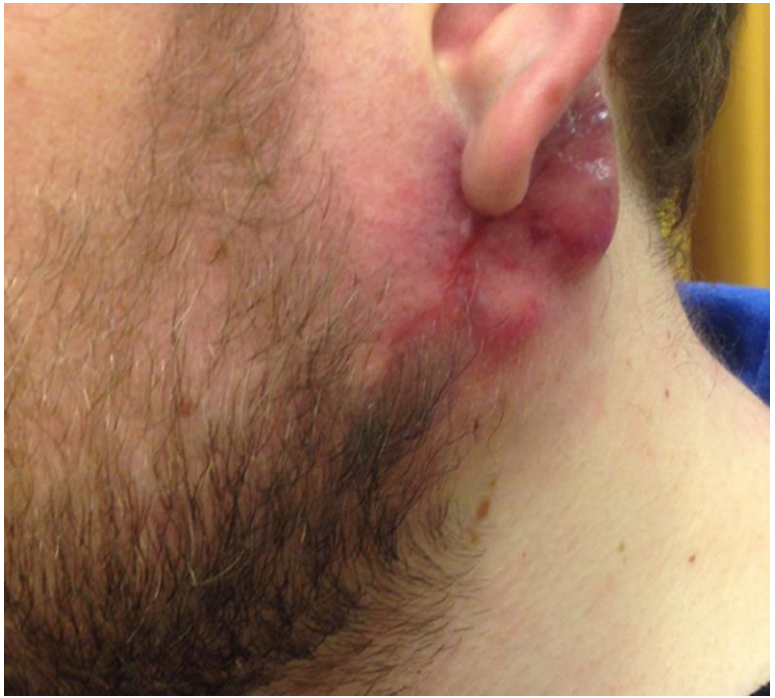
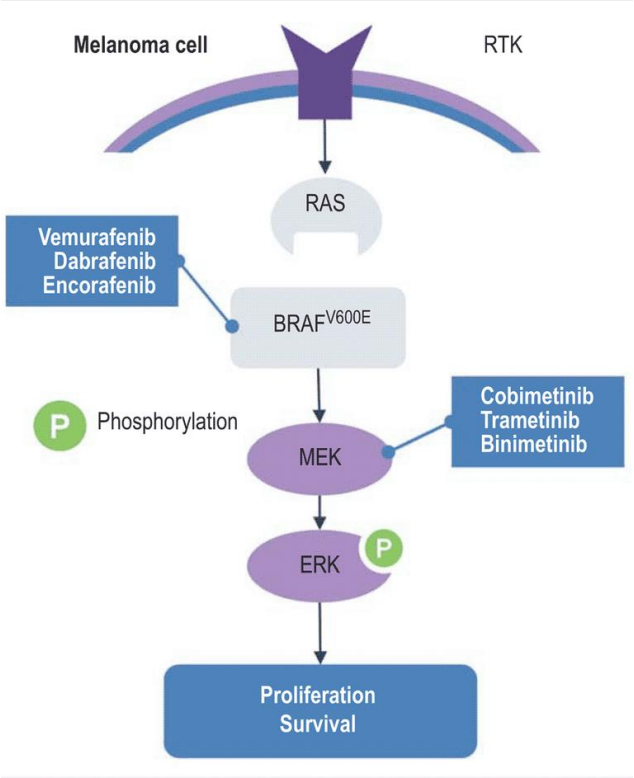




Treatment

- Commenced on combination BRAF and MEK inhibitor, Dabrafenib and Trametinib



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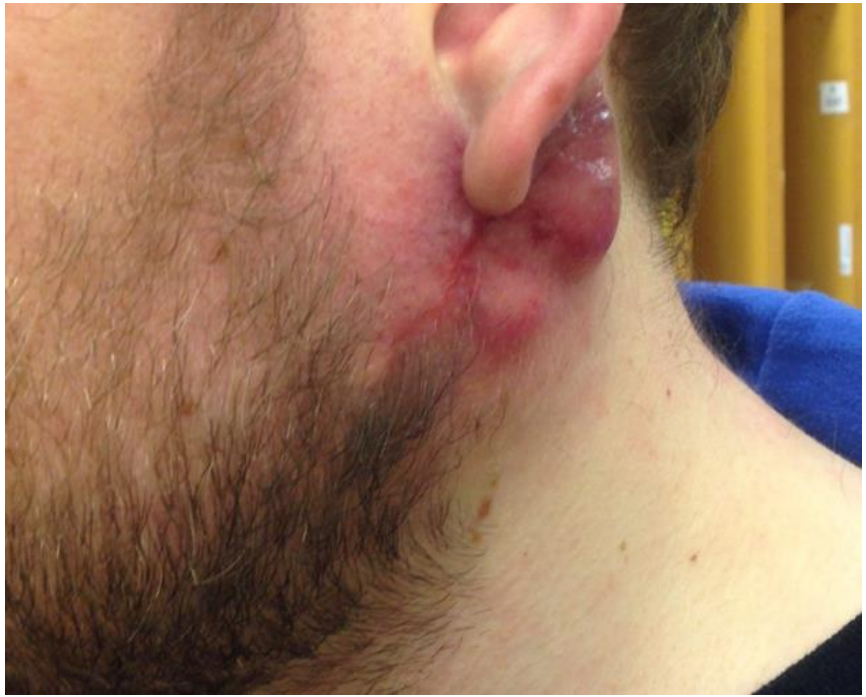
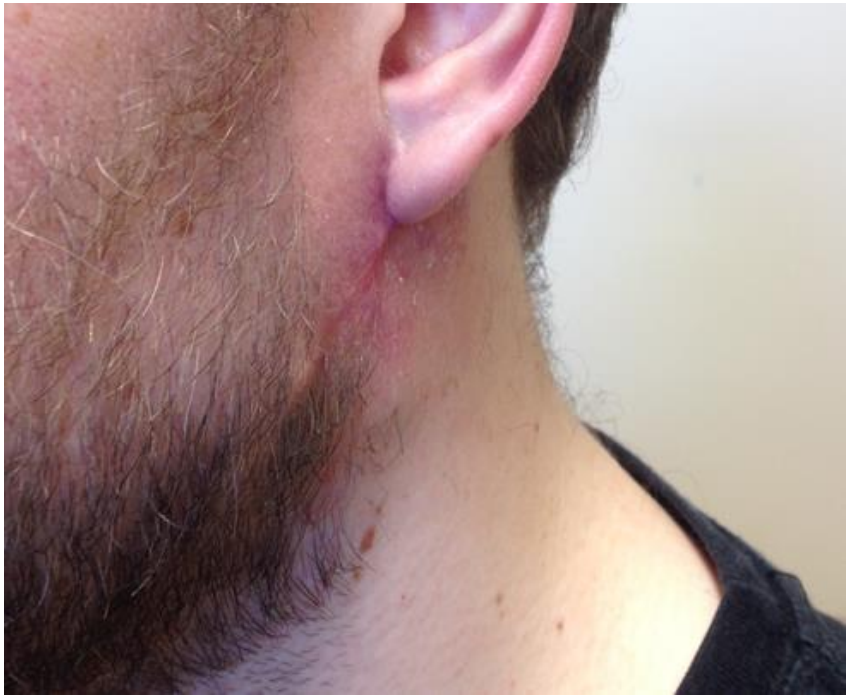


Day 1 BRAF & MEK inhibitor



Day 7 BRAF & MEK inhibitor

Thank you

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