



Ask
the Experts
WEB SERIES
Hosted by Dr. Vivek Subbiah

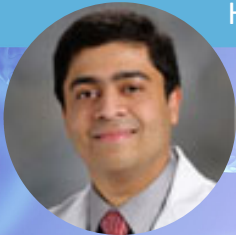
Presented by CEC Oncology and RETpositive.  

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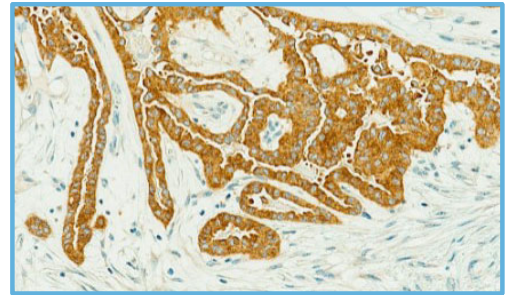
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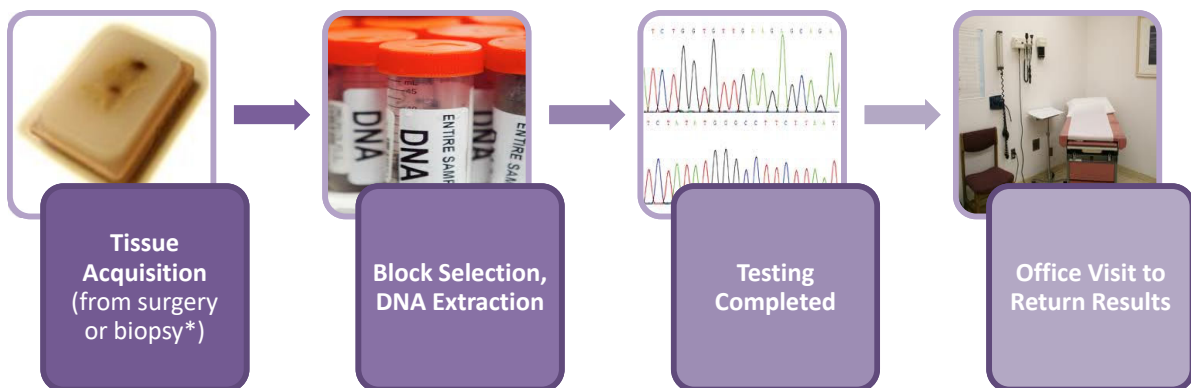


Tests for Somatic Mutations

- Tissue-based tests
 - For one particular mutation (e.g., PCR or immunohistochemistry for *BRAFV600E*)
 - For one particular fusion (e.g., FISH test for *RET* fusion)
 - For hundreds of mutations and fusions (e.g., next generation sequencing)
- Blood-based tests
 - For a single gene mutation (e.g., ddPCR for *RET918* or *BRAFV600E*)
 - For a panel of mutations and some fusions



Tumor Mutation Testing on Tissue



Median Time:

6 calendar days

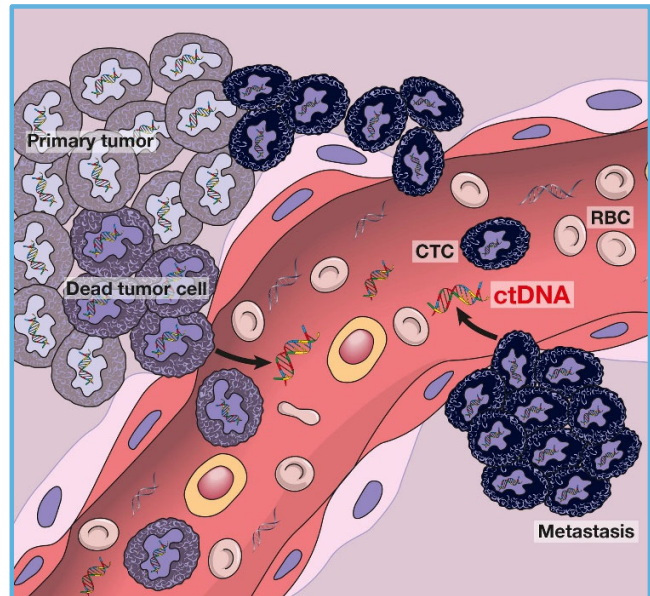
23 calendar days

27 calendar days

*testing can be done on older tissue in storage or a fresh biopsy/surgical specimen

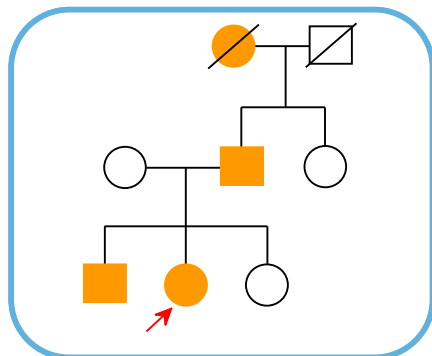
Liquid Biopsy

- Identifies tumor DNA mutations in the blood stream
- Used as a faster and easier way of identifying tumor mutations
- Most commonly used at time of starting chemotherapy or at progression while on chemotherapy
- New tests looking for residual disease serially (i.e., every ~3 months) so that you can predict early when patient no longer responding to treatment
- Problem with liquid biopsy: most thyroid tumors do not shed much DNA into the bloodstream

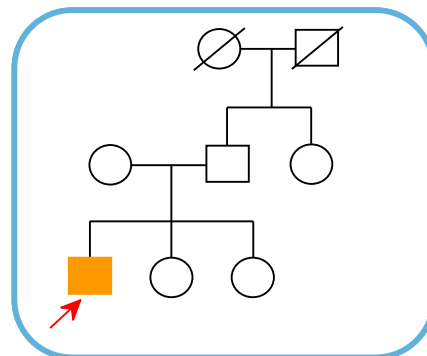


Two Types of *RET* Alterations

Hereditary “germline” *RET* mutation (MEN2)

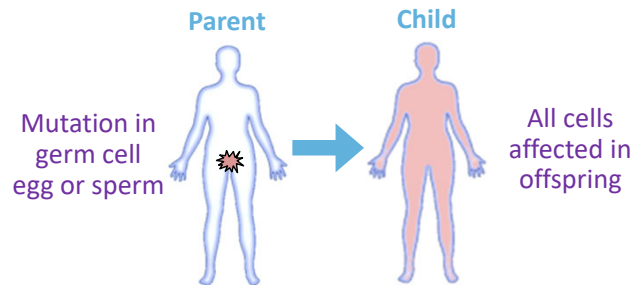
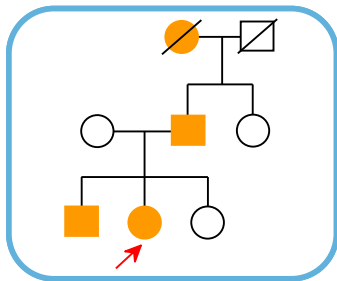


Sporadic *RET* alteration thyroid cancer



MEN2

Hereditary “germline” *RET* mutation (MEN2)



- Mutation exists in the sex cells (eggs/sperm) for reproduction
- 50/50 chance of passing it to children
- >95% of childhood MTC/25% in adults
- Leads to MEN2 (multiple endocrine neoplasia syndrome type 2)
- MEN2 is a syndrome that leads to MTC and other endocrine tumors, such as pheochromocytoma and parathyroid adenomas

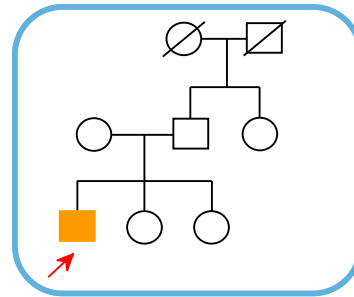
When to Test for Germline *RET* Mutations

- All **MTC patients** should have germline *RET* mutation testing performed—why?
 - Germline *RET* mutations lead to MEN2 (cancer syndrome that includes MTC)
 - To identify family members who are at risk of MEN2
 - MEN2 patients are at very high risk of developing MTC and, therefore, the offspring should also be tested—removing the thyroid before MTC develops is the standard of care
 - “Apparent” sporadic cases (no family history) → 6% have germline mutation

RET Somatic Mutations



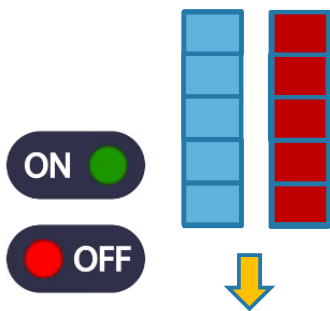
Sporadic *RET* alteration thyroid cancer



- Mutation exists in the tumor cells
- Cannot be passed on to children
- Somatic *RET* mutations and fusions

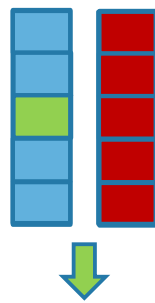
RET Alterations Mutations vs Fusions in Thyroid Cancer

Normal



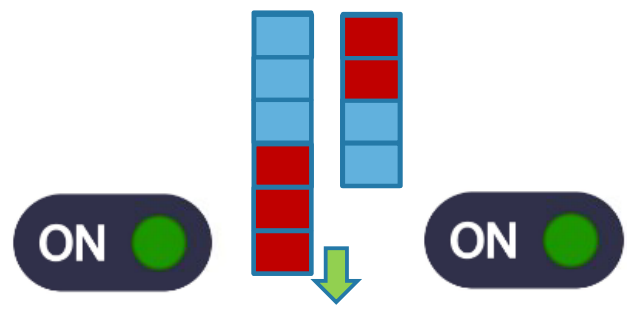
Mutations

- *RET* mutations exist in MTC



Fusions

- *RET* fusions exist primarily in PTC, poorly differentiated and ATC (and lung cancers)



Signal to cells to grow

Patient Case



A 55-year-old male with papillary thyroid cancer presented with vocal cord paralysis and shortness of breath. CT showed large infiltrative left sided thyroid mass with lymph node and lung metastases.



Biopsy of thyroid and lung finds papillary thyroid cancer (PTC).

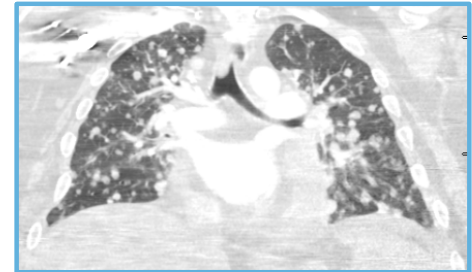


Total thyroidectomy and bilateral neck dissection.



Post-operative clinical information

- Patient requires 4 liters of oxygen
- Thyroglobulin (Tg) 907 ng/mL with Tg antibodies (TgAb) 27 IU/mL



Patient Case

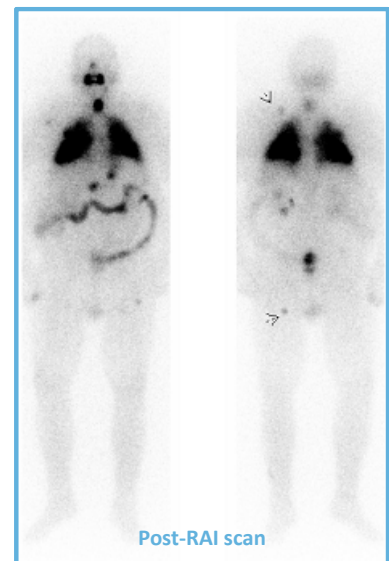


The patient is given 200 mCi of I-131 with good uptake in lungs and mediastinal lymph nodes. Bone mets identified on post-RAI scan (arrows; faint uptake).



Mutation/fusion testing of lung tissue

- BRAF by immunohistochemistry is negative
- NGS → no mutations; RNA for fusions is inadequate for analysis



Patient Case



Thyroidectomy specimen sent for fusions

- *NCOA4-RET* fusion found



After 3 months of observation, more skin metastases appeared, and the patient's oxygen requirement did not decline after RAI.



Patient started on a selective RET inhibitor

- After 6 weeks of therapy, the patient no longer requires oxygen
- Able to ambulate normally
- Thyroglobulin dropped from 907 to 467 ng/mL

