Genetic Testing: Who and Why?

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Objective

To understand the populations in whom genetic testing is performed and why
Agenda

Clinical vs. Molecular Dx
Types of testing
Who to test
Agenda

Clinical vs. Molecular Dx

Types of testing

Who to test
Clinical Utility

- Can the diagnosis be made on clinical features alone?
- How will molecular testing aid in prognosis or treatment?
Clinical vs. Molecular Diagnosis

Achondroplasia
Typically diagnosed by characteristic clinical and radiographic findings

Down syndrome
Physical features may be present, but a molecular test is often needed for confirmation
Agenda

Clinical vs. Molecular Dx

Types of testing

Who to test
Types of testing

- Testing an affected (symptomatic) individual’s germline
  - Diagnostic, Prognostic, Therapeutic

- Testing an asymptomatic individual to determine future risk

- Testing an individual’s germline to benefit family

- Testing of DNA from cancer cells
  - Diagnostic, Prognostic, Treatment response
1. Germline testing in affected individuals

Diagnostic

**Neurofibromatosis Type 1?**
Risk for neurofibromas and optic glioma

**Legius?**
No risk for tumors

**Constitutional Mismatch Repair Deficiency?**
Risk for colon and brain cancer in childhood
1. Germline testing in affected individuals

Prognostic

- Long QT syndrome
  - Syncope
  - Sudden cardiac death

- LQT1 – exercise, emotion
  - Avoidance of strenuous exercise

- LQT2 – emotional stress and auditory stimuli
  - Avoidance of loud noises, e.g. alarm clocks
1. Germline testing in affected individuals

Therapeutic

Plavix

CYP2C19
2. Germline testing to benefit family

FAP

Often a clinical diagnosis, BUT...
3. Germline testing in UNaffected individuals

- No personal history/features
- Family history
- Clinical Utility
4. DNA testing of cancer cells

Cancer of Unknown Primary

http://www.cancer.gov/types/unknown-primary
4. DNA testing of cancer cells

Prognostic

- **Low Risk**
  - Group Average: 6.8%
  - 95% CI: 4.0% - 9.6%

- **Intermediate Risk**
  - Group Average: 14.3%
  - 95% CI: 8.3% - 20.3%

- **High Risk**
  - Group Average: 30.5%
  - 95% CI: 23.6% - 37.4%

Rate of distant recurrence at 10 years (%)

- **Low Recurrence Score Disease**:
  - Indolent
  - Hormone-therapy sensitive
  - Little to no chemotherapy benefit

- **High Recurrence Score Disease**:
  - Aggressive
  - Less sensitive to hormone therapy
  - Large chemotherapy benefit
4. DNA testing of cancer cells

NCCN Guidelines Version 7.2015
Non-Small Cell Lung Cancer

SYSTEMIC THERAPY FOR METASTATIC DISEASE

- Establish histologic subtype with adequate tissue for molecular testing (consider rebiopsy if appropriate)
- Smoking cessation counseling
- Integrate palliative care (See NCCN Guidelines for Palliative Care)

HISTOLOGIC SUBTYPE

- Adenocarcinoma
- Large Cell
- NSCLC not otherwise specified (NOS)

- Squamous cell carcinoma

- EGFR mutation testing (category 1)
- ALK testing (category 1)
- EGFR and ALK testing should be conducted as part of multiplex/next generation sequencing

TESTING RESULTS

- Sensitizing EGFR mutation positive
- ALK positive
- Both sensitizing EGFR mutation and ALK are negative or unknown

- Consider EGFR mutation and ALK testing especially in never smokers or small biopsy specimens, or mixed histology
- EGFR and ALK testing should be conducted as part of multiplex/next generation sequencing

- Sensitizing EGFR mutation positive
- ALK positive
- Both sensitizing EGFR mutation and ALK are negative or unknown

- See First-Line Therapy (NSCL-17)
- See First-Line Therapy (NSCL-18)
- See First-Line Therapy (NSCL-19)
- See First-Line Therapy (NSCL-20)
Who to test

- Proband

- At risk-relatives
  - Mode of inheritance (AR, AD, X-linked)
  - De-novo mutation rate
  - Degree of penetrance
Who to test

- Li-Fraumeni syndrome
  - AD
  - Highly penetrant
  - Management guidelines available

- Rett syndrome
  - X-linked dominant
  - >99% de-novo rate
Thank you