ESMO ADVANCED COURSE ON NTRK GENE FUSION:
The ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

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Vall d’Hebron Institute of Oncology (VHIO), Barcelona

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DISCLOSURE OF INTEREST

- I have served as paid advisor for AstraZeneca, Roche, Amgen, Janssen
- I have participated at symposiums sponsored by Janssen, Astellas, AstraZeneca.
- I have received research funds from AstraZeneca
STANDARDIZING LANGUAGE

**Precision medicine (preferred term)**/personalised medicine. A healthcare approach with the primary aim of identifying which interventions are likely to be of most benefit to which patients based upon the features of the individual and their disease. In cancer, the term usually refers to the use of therapeutics that are expected to confer benefit to a subset of patients whose cancer displays specific molecular or cellular features (most commonly genomic changes and gene or protein expression patterns). Nevertheless, the term also includes the use of prognostic markers, predictors of toxicities and any parameter such as environmental and lifestyle factors that leads to treatment tailoring. Characterisation approaches in the future are expected to encompass a wider range of technologies such as functional imaging.

The European Society for Medical Oncology (ESMO)

**Precision Medicine Glossary**

SEEKING PERSONALIZED OR PRECISION MEDICINE

- Knowing more about the tumor
  - Genomics – molecular stratification of prostate cancer
  - Clonal evolution
  - Precision Imaging

- Knowing more about the patient
  - Social, personal circumstances
  - Comorbidities
  - Expectations, fears

PERSONALIZED MEDICINE is not a new concept, we are just trying to deliver it better by adding more variables (PRECISION)
ESMO PRECISION MEDICINE WORKING GROUP

ESMO members: Interrogated via surveys

Committee: 18 members + two ESMO officers
Define the needs and transform them into projects

11 Projects of recommendations
200 experts (academics, regulatory agencies)
XX e-, v-learnings
MAP conference 400 attendees

Dissemination: ESMO Annual meeting, MAP, Annals of Oncology, ESMO website
AIM OF DEVELOPING NGS TOOLS: IMPROVING PATIENT CARE

- Advances in NGS technology need to be paired by policies to favor implementation in clinical practice: SCALABILITY

- Awareness + Education

- Access to technology could be (potentially) resolved by outsourcing resorts, but interpretation of medical tests is at the core of the physician-patient relationship

- We should prevent NGS becoming a source of health disparity:
  - Access to technology
  - Expertise to implement it
ESCAT: A MULTI-INSTITUTION, INTERNATIONAL EFFORT

Building from previous efforts, accounting for diversity

**ESCAT Project team**
- Debyani Chakravarty
- Rodrigo Dienstmann
- Svetlana Jezdic
- Abel Gonzalez Perez
- Nuria Lopez Bigas
- Charlotte KY Ng
- Philippe L Bedard
- Giampaolo Tortora
- Jean-Yves Douillard
- Eli Van Allen
- Nikki Schultz
- Charles Swanton
- Fabrice Andre
- Lajos Pusztai
- Joaquin Mateo

ESMO Translational Research and Precision Medicine Working Group

ESMO Project Team

ESMO Leadership
BARRIERS FOR IMPLEMENTATION OF GENOMICS INTO ROUTINE CLINICAL PRACTICE

DISEASE-SPECIFIC
- Tumor evolution
- Spatial heterogeneity
- Difficult to access metastatic biopsies
- Predominance of loss-of-function vs oncogenic events
- Small biopsies, fragmented DNA

ASSAYS
- Analytical validation
- Clinical qualification
- Bioinformatics

DATA INTERPRETATION
- Lack of standardized interpretation systems for somatic variants
- New variants discovery
- Data sharing
- Lack of expertise at tumor boards

TECHNOLOGY ACCESS
- Inequalities in healthcare access
- Financial toxicity (insurances)
- Test for individual biomarkers vs multiplexed profiling
BOTTLENECKS

- Patient education
- Sample acquisition
- NGS assay
- Bionformatics
- Reporting
- Tumor board
- Match to available drug

Yield, quality, representative, heterogeneity, evolution
Analytical validation, costs, availability, scalability
Standardization, manual curation
Prioritization, Clinical Relevance (Prognosis, Predictive, Resistance)
Scalability outside academia
Drug availability
Comorbidities, other factors
OBJECTIVES
A framework to rank genomic alterations as targets for cancer precision medicine

- Advance towards **harmonized terminology** in NGS reports
- **Categorize levels of evidence** for precision medicine approaches, irrespectively of national/regional regulatory aspects
- Assist in the interpretation of clinical trial data
- Facilitate discussions at tumor clinical-molecular boards (**clinically-oriented**)
- **Adjust patient expectations** when discussing targeting agents

- Assist clinicians and patients to prioritize precision medicine strategies more likely to impact positively in patient outcome
# Prior Classification Systems

Why do we need another one?

<table>
<thead>
<tr>
<th>Category</th>
<th>Level A</th>
<th>Level B</th>
<th>Level C</th>
<th>Level D</th>
<th>Level E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictive – FDA-approved therapies</td>
<td>There is a validated association between this alteration and response/resistance to this agent for this indication</td>
<td>There is limited clinical evidence (early or conflicting data) for an association between this alteration and response/resistance to this agent in this tumor type</td>
<td>There is clinical evidence for an association between this alteration and response/resistance to this agent in another tumor type ONLY</td>
<td>There is preclinical evidence for an association between this alteration and response/resistance to this agent</td>
<td>There is an inferential association between this alteration and response/resistance to this agent</td>
</tr>
<tr>
<td>Predictive – Therapies in clinical trials</td>
<td>This alteration is used or has been used as an eligibility criterion for clinical trials of this agent or class of agents</td>
<td>There is limited clinical evidence (early or conflicting data) for an association between this alteration and response/resistance to this agent or class of agents in this tumor type</td>
<td>There is clinical evidence for an association between this alteration and response/resistance to this agent or class of agents in another tumor type ONLY</td>
<td>There is preclinical evidence for an association between this alteration and response/resistance to this agent or class of agents</td>
<td>There is an inferential association between this alteration and response/resistance to this agent or class of agents</td>
</tr>
<tr>
<td>Prognostic</td>
<td>There is a validated association between this alteration and prognosis in this tumor type</td>
<td>There is limited evidence for an association between this alteration and prognosis in this tumor type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostic</td>
<td>There is a validated association between this alteration and a diagnosis</td>
<td>There is limited evidence for an association between this alteration and a diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table Examples**

- **FDA-recognized biomarker predictive of response to an FDA-approved drug in this indication**
- **Compelling clinical evidence supports the biomarker as being predictive of response to a drug in another indication, but neither biomarker nor drug are standard care**
- **Standard care biomarker predictive of response to an FDA-approved drug in another indication, but not standard care for this indication**
- **Standard care biomarker predictive of resistance to an FDA-approved drug in this indication**

**Notes**

- **Therapeutic Implications**
  - Includes biomarkers that are recommended as standard care by the NCCN or other expert panels but not necessarily FDA-recognized for a particular indication
  - Possibly directed to clinical trials

- **Hypothetical Therapeutic Implications**
  - Based on preliminary, non-clinical data
## PRIOR CLASSIFICATION SYSTEMS

### Why do we need another one?

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>Clinical implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: Molecular alteration validated in several robust early phase trials or at least one phase III randomized trials</td>
<td>Alteration validated in the disease under consideration, targeted therapies have shown to be ineffective in patients who are lacking the genomic alteration</td>
<td>No evidence that the therapy does not work in the absence of the molecular alteration</td>
<td>Level I molecular alteration, but not in the disease under consideration</td>
<td>A/B: Patients must be treated with the targeted therapy; C: Patients should be considered for clinical trials</td>
</tr>
<tr>
<td>II: Efficacy of targeting molecular alteration suggested in single and underpowered phase I/II trials</td>
<td>Alteration validated in the disease under consideration, targeted therapies have shown to be ineffective in patients who are lacking the genomic alteration</td>
<td>No evidence that the therapy does not work in the absence of the molecular alteration</td>
<td>Level I molecular alteration, but not in the disease under consideration</td>
<td>Patients should be considered for clinical trials testing the targeted therapy</td>
</tr>
<tr>
<td>III: Target suggested by preclinical studies</td>
<td>Preclinical studies include human samples, cell lines and animal models</td>
<td>Preclinical studies that lack either cell lines or animal models</td>
<td>NA</td>
<td>Inclusion in clinical trials is optional</td>
</tr>
<tr>
<td>IV: Target predicted but lack of clinical or preclinical data</td>
<td>Genomic alteration is a known cancer-related gene</td>
<td>Genomic alteration is not known as cancer-related gene</td>
<td>NA</td>
<td>Inclusion in clinical trials is optional</td>
</tr>
</tbody>
</table>

Andre et al, Ann Oncol 2014

- Different clinical attitude within the same tier
- Same recommendation for different tiers
LEVERAGE FOR ESCAT: ROOM FOR IMPROVEMENT

Why do we need another one?

- Randomized clinical trial data as stratification criteria
- Efficacy (PFS/OS) + Antitumor activity (Response)
- Magnitude of benefit
- Evidence for the match in other tumor types
- Evidence in other biologically similar mutations
- Facilitating dynamic classification as new data emerges

ACTIONABILITY + CLINICAL BENEFIT

- FDA/EMEA registration status
- One Tier = One Clinical Action
- Not aiming to judge pathogenicity of mutations (biological relevance)
- Not based the drug alone but in the match
A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

**ESMO SCALE FOR CLINICAL ACTIONABILITY OF MOLECULAR TARGETS (ESCAT)**

**Tier I**

<table>
<thead>
<tr>
<th>Evidence tier</th>
<th>Required level of evidence</th>
<th>Clinical Class</th>
<th>Clinical Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>General use</td>
<td>I: Alteration-drug match is associated with improved outcome in clinical trials</td>
<td>I-A: Prospective, randomized clinical trials show the alteration-drug match in a specific tumour type results in a clinically meaningful improvement of a survival endpoint. I-B: Prospective, non-randomized clinical trials show that the alteration-drug match in a specific tumour type, results in clinically meaningful benefit (as defined by ESMO MCBS 1.1) I-C: Clinical trials in other tumour types or basket clinical trials show clinical benefit associated with the alteration-drug match, with similar benefit observed across tumor types</td>
<td>Drug administered to patients with the specific molecular alteration has led to improved clinical outcome in prospective clinical trial</td>
</tr>
</tbody>
</table>
ESMO MAGNITUDE OF CLINICAL BENEFIT SCALE (ESMO-MCBS)

• AIM: to provide a validated and reproducible tool to assess the magnitude of clinical benefit from new cancer therapies

• Integrate both relative and absolute benefit
  • Considering the LL95%CI rule aims to penalize wide CI: small trials
  • Considering the mean absolute benefit aims to penalize trials that are so big that detect non-clinically relevant differences

• Adjust clinical relevance of benefit based on prognosis

• Impact of PFS/OS in different tumour types

• Integrate QOL data into evaluation
ESMO MAGNITUDE OF CLINICAL BENEFIT SCALE (ESMO-MCBS)

Maximal preliminary scores

Treatments with curative intent (form 1)
- >5% Improvement of survival at ≥3-year follow-up
- Improvements in PFS alone HR <0.80 (primary end point) in studies without mature survival data

Treatments with non-curative intent (form 2)

Primary outcome OS (form 2a)
- Control ≤12 months
  - HR ≤0.65 AND gain ≥3 months OR
  - Increase in 2-year survival alone ≥10%
- Control >12 months
  - HR ≤0.70 AND gain ≥5 months OR
  - Increase in 3-year survival alone ≥10%

Primary outcome PFS (form 2b)
- Control ≤6 months
  - HR ≤0.65 AND gain ≥1.5 months
- Control >6 months
  - HR ≤0.65 AND gain ≥3 months

DESIGN: Power Target Benefit

STEP 2

Threshold for the HR of the primary Endpoint
Relative & Absolute Benefit Thresholds

STEP 3

Severe toxicities
Grade 3-4 toxicities bothering patients
QoL

STEP 1

Strength of the randomised Evidence

Preliminary grade on the scale

Final adjusted grade

ESMO MCBS evaluation

Curative

Non-curative

Curative - Evaluation form 1: for new approaches to adjuvant therapy or new potentially curative therapies

Non-curative - Evaluation forms 2a, b or c: for therapies that are not likely to be curative
The ESMO Magnitude of Clinical Benefit Scale uses a rational, structured and consistent approach to derive a relative ranking of the magnitude of clinically meaningful benefit that can be expected from a new anti-cancer treatment.

There are several evaluation forms, which can be downloaded below:

### Evaluation form 1

For new approaches to adjuvant therapy or new potentially curative therapies

Hyper mature data from studies that were un-blinded after compelling early results with subsequent access to the superior arm are contaminated, subsequently late intention to treat (ITT) follow-up data are not evaluable.

### Evaluation form 2a

For therapies that are not likely to be curative with primary endpoint of OS with separate sheets for:
- IF median OS with the standard treatment is <12 months
- IF median OS with the standard treatment is >12 months, <24 months
- IF median OS with the standard treatment is >24 months

### Evaluation form 2b

For therapies that are not likely to be curative with primary endpoint PFS with separate sheets for:
- IF median PFS with standard treatment is <6 months
- IF median PFS with standard treatment is >6 months

### Evaluation form 2c

For therapies that are not likely to be curative with primary endpoint other than OS or PFS or equivalent (non-inferiority) studies

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https://www.esmo.org/Guidelines/ESMO-MCBS/Scale-Evaluation-Forms-v1.0-v1.1/Scale-Evaluation-Forms-v1.1
NTRK FUSIONS – ESCAT TIER I CLASSIFICATION

- High prevalence in very rare cancers; conducting phase III trials is not feasible
- Very low prevalence in common cancers
- Similar level of antitumor activity observed across tumour types in basket trials
- Durability of responses (OS is difficult to evaluate in non-randomized trials)
# ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT)

## Tier II

<table>
<thead>
<tr>
<th>Evidence tier</th>
<th>Required level of evidence</th>
<th>Clinical Class</th>
<th>Clinical Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigational</td>
<td>II: Alteration-drug match is associated with antitumor activity, but magnitude of benefit is unknown</td>
<td>II-A: Retrospective studies show patients with the specific alteration in a specific tumor type experience clinically meaningful benefit with matched drug compared to alteration-negative patients</td>
<td>Drug administered to a molecularly defined patient population is likely to result in clinical benefit in a given tumor type, but additional data is needed</td>
</tr>
<tr>
<td></td>
<td>II-B: Prospective clinical trial(s) show the alteration-drug match in a specific tumor type results in increased responsiveness when treated with a match drug, however no data currently available on survival endpoints.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT)

#### Tier III

<table>
<thead>
<tr>
<th>Evidence tier</th>
<th>Required level of evidence</th>
<th>Clinical Class</th>
<th>Clinical Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothetical</td>
<td>III: Alteration-drug match suspected to improve outcome based on clinical trial data in other tumor type(s) or with similar molecular alteration</td>
<td>III-A: Clinical benefit demonstrated in patients with the specific alteration (as tiers I and II above) but in a different tumor type. Limited/absence of clinical evidence available for the patient-specific cancer type or broadly across cancer types</td>
<td>Drug, previously shown to benefit molecularly defined subset in another tumor type, or with a molecular alteration expected to cause a similar effect. Clinical trials to be discussed with patients.</td>
</tr>
<tr>
<td></td>
<td>III-B: An alteration with expected similar biological functional impact as a match with level I/II, but without clinical data.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Larotrectinib

Drilon et al, NEJM 2018
TIER III-A AND BASKET TRIALS: BRAF INHIBITORS EXAMPLE

Hyman et al, NEJM 2015

Chapman et al, NEJM 2011
TIER III-A AND BASKET TRIALS: PARP INHIBITORS EXAMPLE

Jonsson et al, Nature 2019
## ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT)

### Tier IV

<table>
<thead>
<tr>
<th>Evidence tier</th>
<th>Required level of evidence</th>
<th>Clinical Class</th>
<th>Clinical Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothetical</td>
<td>IV-A: Evidence that the alteration or a functionally similar alteration alters drug sensitivity in preclinical in-vitro or in-vivo models.</td>
<td>Actionability is predicted based on preclinical studies, no conclusive clinical data available</td>
<td>Treatment should only be considered in the context of early clinical trials.</td>
</tr>
<tr>
<td></td>
<td>IV-B: Actionability predicted in silico</td>
<td></td>
<td>Lack of clinical data should be stressed to patients</td>
</tr>
</tbody>
</table>

- **IV**: Pre-clinical evidence of actionability
## Tier V

<table>
<thead>
<tr>
<th>Evidence tier</th>
<th>Required level of evidence</th>
<th>Clinical Class</th>
<th>Clinical Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comb</td>
<td>Alteration-drug match is associated with objective response, but without clinically meaningful benefit</td>
<td>Prospective study show that targeted therapy is associated with objective responses, but this does not lead to improved outcome</td>
<td>Drug is active but does not prolong PFS or OS, probably in part due to mechanisms of adaptation</td>
</tr>
</tbody>
</table>
ESMO SCALE FOR CLINICAL ACTIONABILITY OF MOLECULAR TARGETS (ESCAT)

Tier X

<table>
<thead>
<tr>
<th>Evidence tier</th>
<th>Required level of evidence</th>
<th>Clinical Class</th>
<th>Clinical Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>X: Proven lack of</td>
<td>Evidence that the genomic alteration is not actionable</td>
<td>Conclusive clinical evidence exists for a genomic alteration not to be useful to</td>
<td>The result of the biomarker assay should not be taken into account for clinical decision</td>
</tr>
<tr>
<td>clinical value</td>
<td></td>
<td>select patients for a particular targeted agent</td>
<td></td>
</tr>
</tbody>
</table>

The lack of data demonstrating value is not the same than having data demonstrating lack of value!
A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

ESMO SCALE FOR CLINICAL ACTIONABILITY OF MOLECULAR TARGETS (ESCAT)

Strengths and Limitations

• ESCAT is clinically-oriented (clinical action is the endpoint)

• Clinical trial data as the center of ESCAT

• Provides a shared vocabulary to physicians, patients, drug development stakeholders, NGS developers

• ESCAT goes beyond regulatory status, regulatory markets: creating a joint framework

ROOM FOR IMPROVEMENT:

• Easier rules to upgrade/downgrade targets

• Target vs biomarker

• Account for tumour type particularities on magnitude of benefit (PFS, OS)

• Improve assessment of combination of targets and prioritization of same-level targets

• Prognostic vs predictive, positive vs negative predictive value (response/resistance)
ESMO SCALE FOR CLINICAL ACTIONABILITY OF MOLECULAR TARGETS (ESCAT)

Next steps

Describe the landscape of targets and rank according to ESCAT across tumor types

Evaluate cost-efficiency, reproducibility

Implementation of ESCAT in NGS reporting from academic and private partners – audit experience, virtues and room for improvements

Integration with bioinformatics tools and public resources (on going work at VHIO and within CCE Consortium and others)
<table>
<thead>
<tr>
<th>Alterations</th>
<th>Alteration considered</th>
<th>Alteration not considered</th>
<th>LOE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERRB2</td>
<td>Focal amplification (DNA copy number ≥6; size ≤10 Mb)</td>
<td>DNA gain (DNA copy number &lt;6)</td>
<td>IA</td>
<td>Romond et al. [13], Fehrenbacher et al. [14]</td>
</tr>
<tr>
<td>Germine BRCA1/2 mutations</td>
<td>Truncated mutations: InDel, splice-site, nonsense (except known truncating polymorphic variant, i.e. BRCA2 K3326X), Rare known inactivating missense mutations (pathogenic variant class S)</td>
<td>Most of missense variants (classes 1–4)</td>
<td>IA</td>
<td>Robson et al. [17], Litton et al. [18]</td>
</tr>
<tr>
<td>PIK3CA mutations</td>
<td>Major hot-spot activating missense mutations (E542K, E545K/A, H1047R/L)</td>
<td>Other missense mutations, Truncated mutations (InDel, splice-site, nonsense)</td>
<td>IA</td>
<td>Andre et al. [19], Hortobagyi et al. [20]</td>
</tr>
<tr>
<td>Microsatellite instability (MSI)</td>
<td></td>
<td></td>
<td>IC</td>
<td>Cortes-Ciriano et al. [21], Le et al. [22], Pembrolizumab package insert [23]</td>
</tr>
<tr>
<td>NTRK translocations</td>
<td></td>
<td></td>
<td>IC</td>
<td>Amini et al. [24], Dillan et al. [25]</td>
</tr>
<tr>
<td>ESRT1 mutations</td>
<td>Hot-spot activating missense mutations (E380Q, Y537S/C, D538Q)</td>
<td>Other missense mutations, Truncated mutations (InDel, splice-site, nonsense)</td>
<td>IA</td>
<td>Friebens et al. [26]</td>
</tr>
<tr>
<td>PTEN loss</td>
<td>Homozygous deletions, Loss-of-function mutations: truncated mutations and known inactivating missense mutations (Ex: R130Q/G)</td>
<td>Other missense mutations</td>
<td>IA</td>
<td>Schmait et al. [27]</td>
</tr>
<tr>
<td>AKT1 mutations</td>
<td>F17K</td>
<td>Other mutations</td>
<td>IB</td>
<td>Hyman et al. [28], Emma Dean et al. [29]</td>
</tr>
<tr>
<td>ERRB2 mutations</td>
<td>Hot-spot activating missense mutations (eg, S510F/Y, L775S, V777L), In-frame insertion exon 3 (Ex: Y772, K775dup)</td>
<td>Not hot-spot missense mutations, Truncated mutations (InDel, splice-site, nonsense)</td>
<td>IB</td>
<td>Hyman et al. [30], Ma et al. [31]</td>
</tr>
</tbody>
</table>

**EXAMPLE:** METASTATIC BREAST CANCERS

Number to test to get benefit: 20 (5% benefit)
Number to test to get drug access: 2 (50% benefit)
# EXAMPLE: METASTATIC LUNG CANCERS

<table>
<thead>
<tr>
<th>Alteration</th>
<th>Alteration considered</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>Mutation (Del19, L858R), Acquired T790M exon 20</td>
<td>IA</td>
</tr>
<tr>
<td>ALK</td>
<td>Rearrangement</td>
<td>IA</td>
</tr>
<tr>
<td>BRAF</td>
<td>V600E mutations</td>
<td>IB</td>
</tr>
<tr>
<td>ROS1</td>
<td>Rearrangements</td>
<td>IB</td>
</tr>
<tr>
<td>RET</td>
<td>Rearrangements</td>
<td>IIB</td>
</tr>
<tr>
<td>NTRK</td>
<td>Rearrangements</td>
<td>IC</td>
</tr>
<tr>
<td>MET</td>
<td>Mutation exon 14 skipping / amplification</td>
<td>IB / IIB</td>
</tr>
<tr>
<td>HER2</td>
<td>Mutation / amplification</td>
<td>IIB</td>
</tr>
<tr>
<td>NRG1</td>
<td>Fusion</td>
<td>IVA</td>
</tr>
<tr>
<td>KRAS</td>
<td>Mutation</td>
<td>X</td>
</tr>
<tr>
<td>STK11</td>
<td>Mutation</td>
<td>X</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>Mutation / amplification</td>
<td>X</td>
</tr>
</tbody>
</table>
| NRG1       | Fusion                                                     | IVA???

Number to test to get benefit: 6-7 (15% benefit)
TAKE HOME MESSAGES

- ESCAT provides an harmonized system to report clinical relevance of genomic findings

- Main aim is to facilitate interpretation of NGS reports for physicians and patients (improve patient care, manage expectations, facilitate communication)

- A step towards implementing precision medicine in routine clinical practice

- NTRK fusions are a example of a targetable Tier I finding

- Emerging data should be incorporated into rankings – dynamic shared databases maybe better than traditional publication format to disseminate ESCAT
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Building from previous efforts, accounting for diversity

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