Expert Consensus on the Testing and Medical Management of PIK3CA-Related Overgrowth Spectrum

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Introduction

PIK3CA-related overgrowth spectrum (PROS) is a group of disorders caused by somatic mutations in the PIK3CA gene. PIK3CA is also a commonly mutated gene in many solid cancers, including breast, ovarian, and colorectal cancers.

A PIK3CA inhibitor (alpelisib) has been approved for the treatment of breast cancer and early evidence shows that it may be effective for patients with PROS.

Objectives

In 2013, a panel of researchers and patient representatives met at the National Institutes of Health (NIH) to discuss the emerging group of conditions caused by PIK3CA mutations. A resulting 2015 publication named and defined PIK3CA-related overgrowth spectrum (PROS) and made recommendations for genetic testing.

We conducted an expert RAND/UCLA Delphi panel **to update these 2015 guidelines and describe PROS severity classification, testing, and medical management.**

Methods

We conducted an expert RAND/UCLA Delphi panel, the steps of which are outlined in Figure 1.

1. We convened a diverse, experienced 13-member panel and reviewed evidence on PROS diagnosis and treatment.
2. We collaboratively developed a rating form made up of 217 clinical scenarios having mild/moderate/severe presentations based on functional impairment, a reduction in quality of life (QOL), and risk of death (Table 1).
3. Before and after a virtual meeting, panelists rated each scenario's disease severity and the appropriateness of whether or not to test for a mutation and of prescribing mTOR/PI3K/AKT inhibitors.
4. At the meeting, panelists discussed areas of disagreement.
5. After the meeting, consensus statements summarizing the group opinion were drafted.

Figure 1. The RAND/UCLA Delphi Panel Process

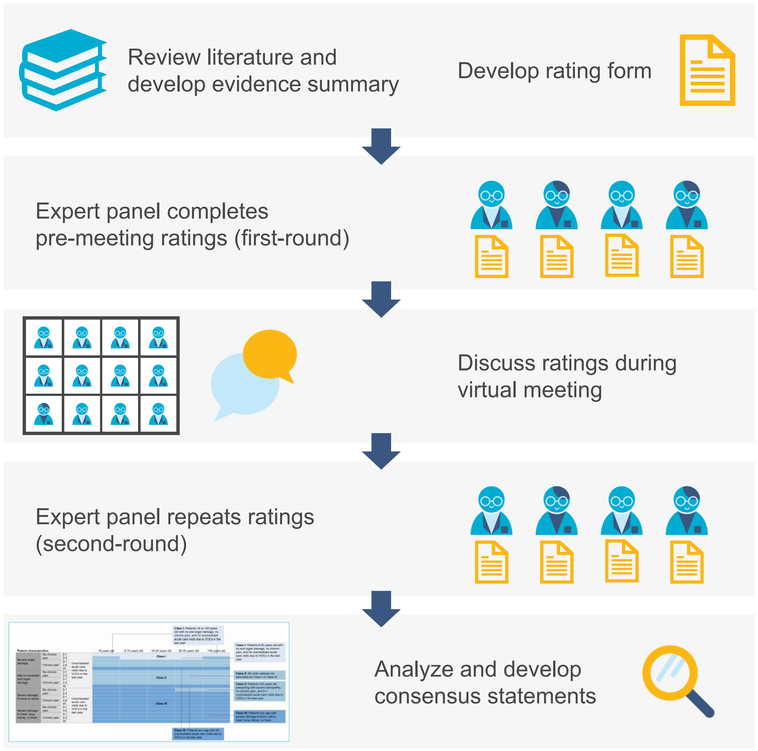

Table 1. Severity Classification Framework

Scenarios described patients that were mildly, moderately, or severely affected by PROS based on functional impairment, a reduction in QOL, and risk of death.

	Mildly affected	Moderately affected	Severely affected
Functional impairments[a]	In adults: Some impact on instrumental activities of daily living (iADLs)[b], e.g., needs to be accompanied on shopping trips, prepares meals if supplied with ingredients, travels when accompanied by another, takes medication if prepared in advance in separate dosage. Can carry out activities of daily living (ADLs)[c] without supervision or assistance. In children: No more than slight impairment in functioning at home, at school, or with peers. May be some limitations walking long distances or balancing.	In adults: Cannot carry out iADLs, e.g., does not use phone, unable to shop, needs to have meals prepared and served, does not travel. Some impact on ADLs, e.g., needs help with bathing, dressing, cleaning self, feeding. May miss work/school occasionally, associated with some limits to mobility that can be compensated (e.g., use other hand to carry out ADLs). In children: Some interference in social functioning at home, at school, or with peers. Can sit with some external support, may use mobility device when walking.	In adults: Cannot carry out iADLs or ADLs, e.g., cannot manage basic physical needs, unable to attend work/school. In children: Needs constant supervision (24-hour care) due to gross impairment in communication, cognition, affect, or personal hygiene. Severe limitations in head and trunk voluntary control, requires physical assistance sitting.
QOL reduction, e.g., fatigue, depression/anxiety, pain, sleep disturbances	No or limited impact on QOL	Some reduction in QOL (e.g., pain, depression/anxiety, fatigue that does not interrupt ADLs)	Significant reduction in QOL (e.g., pain, depression/anxiety, fatigue that interrupts ADLs)
Risk of death	None	Increased risk of complications but not of death	Increased risk of death
Examples of clinical presentations	• Isolated, well-circumscribed lymphatic malformation • Isolated (superficial) capillary-venous malformation • Organ overgrowth without impaired function (e.g., splenic enlargement without hypersplenism) • Musculoskeletal overgrowth not requiring surgical intervention	• Cutaneous lymphatic leakage • Bleeding that results in anemia and requires only oral iron support • Organ overgrowth with impaired function (e.g., splenic enlargement with hypersplenism) • Contracture or joint involvement causing anatomic impairment that has some impact on ADLs	• Paraspinal high flow or other high-risk lesion • Inflammatory flare-ups and/or infections resulting in hospitalization • Increased risk of embolism due to a malformation with connection to deep venous system (i.e., large, ectatic, or anomalous) • Compromised airway (e.g., due to overgrowth or lymphatic malformation) • Intractable seizures despite medication (e.g., may be due to brain overgrowth)

Results

The panel developed clinical presentations and endorsed the **severity classification framework** (Table 1).

Testing

In the second-round, panelists agreed on 100% of ratings on when to test for a mutation:

- Except when the potential clinical harms outweigh the benefits or when costs make it unreasonable to do, panelists agreed it is appropriate to test for a PIK3CA mutation in **every moderately/severely affected patient**.
- The panel also agreed it is appropriate to test for a mutation in **mildly affected patients** in certain circumstances including when medical therapy with a PI3K or AKT inhibitor is being considered, when biopsy tissue has been or will be obtained during a planned surgery, and when the result would change a plan for surveillance

Medical Management

In the second-round, panelists agreed on 74% of ratings on medical therapy:

- Panelists agreed that it may be appropriate to consider an **mTOR inhibitor** in some severely affected patients and some moderately affected children or adolescents/adults with progressive disease.
- Although clinical trials have only recently begun and evidence is still limited, the panel agreed it may be appropriate to consider treatment with a **PI3K or AKT inhibitor** on a compassionate use basis in some cases, for example:
  - In severely affected children or adolescents/adults with a confirmed PIK3CA mutation, or in those without a confirmed mutation but with progressive disease.
  - In severely affected infants (≤2 years old) with a confirmed mutation and progressive disease.
- The panel did not come to a consensus on the use **of PI3K or AKT inhibitors** in mildly/moderately affected patients.

Conclusions

These recommendations represent the consensus of 13 experts informed by literature and experience. Future research should validate this guidance using clinical data. Once validated, we hope these recommendations will improve outcomes for patients with PROS.

Limitations

- The quality of the data underlying this consensus was quite varied, and new developments in diagnosis or treatment could render the panel's conclusions obsolete.
- Although all panelists had significant experience in the field and were drawn from a diversity of backgrounds and geographic regions, 13 experts cannot represent the full experience of clinicians who work in this field. Different groups of experts may have reached different conclusions.

Table Footnotes

[a]In adults, functional impairment is based on the Lawton & Brody (1969) Instrumental Activities of Daily Living (iADL) Scale and the Katz ADL Index (1970). In children, functional impairment is based on the Gross-Motor Function Classification System and the Children's Global Assessment Scale (Schaffer et al. Arch Gen Psychiatry 1983).
[b]More complex activities required for independent functioning in community settings (e.g., shopping, cooking, managing finances).
[c]Basic activities required for survival (e.g., eating, bathing, toileting).

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