OPEN

Journal of Vascular Anomalies
An open access multidisciplinary journal
ISSVA

RAND/UCLA Modified Delphi Panel on the Severity, Testing, and Medical Management of PIK3CA-Related Spectrum Disorders (PROS)

Michael S Broder[a], Denise M Adams[b], Guillame Canaud[c], Christy Collins[d], Kristen Davis[e], Ilona J. Frieden[f], Sarah N Gibbs[a], Adrienne M Hammill[g], Kim M Keppler-Noreuil[h], Taizo A Nakano[i], Anthony Penington[j], Siddharth Srivastava[k], Megha M Tollefson[l], Matthew L Warman[k]

Objective(s): PIK3CA-related overgrowth spectrum (PROS) is a group of disorders caused by somatic variants in the *PIK3CA* gene. We aimed to update recommendations on the severity classification, testing, and medical management of patients with PROS.

Methods: Using validated consensus methodology, we convened a 13-member panel in 2020 and reviewed current evidence on how to diagnose and treat PROS. The panel was asked to rate the level of disease severity, and the appropriateness of whether to test for a mutation and medical therapy in 217 patient scenarios before a virtual meeting. Panelists discussed areas of disagreement and completed ratings following the meeting.

Results: The panel developed clinical presentations and endorsed the disease severity framework defined by functional impairment, a reduction in quality of life, and risk of death. Panelists agreed it is appropriate to test for a *PIK3CA* gene variant in every moderately/severely affected patient. Panelists agreed it may be appropriate to consider an mammalian (mechanistic) target of rapamycin inhibitor in some severely affected patients and some moderately affected patients with progressive disease. Although clinical trials have only recently begun and the evidence remains limited, panelists also agreed it may be appropriate to consider treatment with phosphoinositide 3-kinase/serine/threonine protein kinase inhibitors in severely affected patients with a confirmed *PIK3CA* variant or without a confirmed variant but with progressive disease.

Conclusion: These recommendations represent the consensus of experts informed by published 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.

Keywords: Delphi panel, PIK3CA-related spectrum disorders, severity classification

[a]PHAR (Partnership for Health Analytic Research); [b]Children's Hospital Philadelphia; [c]Necker-Enfants Malades Hospital; [d]M-CM Network; [e]CLOVES Syndrome Community; [f]UCSF Benioff Children's Hospital; [g]Cincinnati Children's Hospital Medical Center and the University of Cincinnati College of Medicine; [h]University of Wisconsin- Madison, School of Medicine & Public Health; [i]Children's Hospital Colorado; [j]The Royal Children's Hospital Melbourne, Murdoch Children's Research Institute; [k]Boston Children's Hospital, Harvard Medical School; and [l]Mayo Clinic

Financial Disclosure: The authors declare that they have no conflicts of interest with regard to the content of this report. Authors have completed ICMJE forms.

Previous Presentations: Poster presented at the CLOVES Syndrome Community International Scientific Meeting for PIK3CA Related Conditions; Oct 28–29, 2021.

Level of evidence: 5, Expert opinions based on non-systematic reviews of results or mechanistic studies

Correspondence Michael S Broder, MD, 280 S. Beverly Drive, Suite 404, Beverly Hills, CA 90212. (mbroder@pharllc.com).

Journal of Vascular Anomalies (2023) 4:e067

Received: 27 September 2022; Accepted 28 April 2023

Published online 31 May 2023

DOI: 10.1097/JOVA.0000000000000067

Introduction

PIK3CA-related overgrowth spectrum (PROS), or PIK3CA-related spectrum disorders, is a group of disorders usually caused by somatic variants in the *PIK3CA* gene including fibroadipose overgrowth, congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal (CLOVES) syndrome, hemihyperplasia multiple lipomatosis, Klippel-Trenaunay syndrome, macrodactyly, and megalencephaly-capillary malformation.[1] PROS disorders have an asymmetric, patchy presentation and, with the exception of some megalencephaly-capillary malformation cases, lack familial recurrence (somatic).[2] The observed wide phenotypic spectrum is a result of mosaicism;[3] the timing and location of the mutation, tissue distribution, and stage of embryogenesis;[4] and mechanistic differences among *PIK3CA* alleles.[5,6]

PROS disorders often have overlapping clinical features that include both tissue-specific localized effects and pleiotropic presentation.[1] Overgrowth may occur in isolated or multiple tissues such as skin, bone, muscle, adipose tissue, neural tissue, and blood or lymph vessels.[7] Deformities may present prenatally, at birth, or sometimes during puberty, and become

accentuated with growth. Although the data are quite limited, clinical experience suggests most presentations are associated with significant morbidity and decreased quality of life.[8]

PIK3CA is also a commonly mutated gene in many solid cancers, including breast, ovarian, and colorectal cancers.[9] Alpelisib has been approved for the treatment of patients with a *PIK3CA* mutation in HR+/HER2– advanced breast cancer[10] and early evidence shows that it may be effective for patients with PROS.[11]

In 2013, a panel of researchers and patient representatives met at the National Institutes of Health (NIH) to develop a consensus on diagnostic categories for PROS and determine when a patient should be tested for the *PIK3CA* variant.[1] The NIH used an unstructured consensus panel process. In 2020, we convened a new, international panel using the RAND/University of California, Los Angeles (UCLA) modified Delphi panel method, a structured consensus methodology. Our goal was to update the recommendations on the severity classification and testing and develop new recommendations for the medical management of individuals with PROS.

Materials and methods

We used the RAND/UCLA modified Delphi panel method, a formal group consensus process that systematically and quantitatively combines expert opinion and evidence by asking panelists to rate, discuss, then re-rate items. The steps include the selection of panelists, generation of a rating form, a review of the literature, a first-round survey, typically an in-person meeting where panelists discuss areas of disagreement, final ratings and analysis of those ratings, and the development of a written summary of areas of agreement. The method implicitly recognizes that each clinical situation is different, with its own set of complex characteristics. In practice, many other clinical and nonclinical factors beyond those addressed in such a panel will affect the decision to test for a variant or consider medical therapy. The consensus statements that result from the use of a RAND/UCLA modified Delphi panel method are in no way intended to supersede physician decision-making and are intended only as general guidance.

We convened a 13-member panel comprised of 11 physicians and 2 patient advocates in 2020. Physicians had a variety of clinical backgrounds, including hematology/oncology (n = 3), genetics (n = 2), dermatology (n = 2), plastic surgery (n = 1), neurology (n = 1), nephrology (n = 1), and radiology (n = 1). The 2 patient advocates were leaders of patient advocacy organizations on PROS conditions (CLOVES and megalencephaly-capillary malformation). All panelists had experience with a variety of PROS conditions. Eleven panelists were from the United States: 6 from the Northeast (MA, ME, NY, PA), 3 from the Midwest (MN, OH, WI), and 2 from the West (CA, CO). Two panelists were from outside the United States (1 from France and 1 from Australia). Seven were female. The panelists had an average of 13 (range 3–31) years working with PROS disorders and physicians had an average of 20 (range 4–37) years of clinical experience. Panelists were compensated for their time by Novartis Pharmaceutical Corporation as part of their ongoing research on PROS and alpelisib. Novartis provided input on the composition of the panel but did not provide input on the methodology or results of the panel. The study did not involve human subjects and was therefore not subject to institutional review board approval.

Panelists and researchers collaboratively developed a rating form made up of patient scenarios through a series of individual phone interviews. Using panelist experience treating the conditions, we developed scenarios that broadly described patients with mild, moderate, and severe phenotypes with the distinction based on the level of functional impairment, quality of life reduction, and risk of death. For example, to be labeled "mildly" affected, patients with PROS should not have an increased risk of complications nor death from their disease manifestations, "moderately" affected patients should have an increased risk of complications but not death, and "severely" affected patients should have an increased risk of death. Similar criteria were established for functional impairment and quality of life. We also developed examples of clinical presentations for each level of severity (Table 2). These were intended to help panelists imagine the range of patients affected by PROS.

Researchers conducted a targeted review of the literature to develop a summary of the current evidence on the diagnosis, classification, and treatment of PROS. The summary included the diagnostic and testing criteria developed by the 2013 NIH panel,[1] a description of the various clinical presentations and potential complications of the phenotypes, and a review of the completed and ongoing clinical trials of targeted medical therapies used in PROS (including mammalian (mechanistic) target of rapamycin [mTOR], phosphoinositide 3-kinase [PI3K], and serine/threonine protein kinase [AKT] inhibitors). This summary was intended to provide panelists with a review of the current evidence on the diagnosis, testing, and treatment of PROS, as well as additional examples of phenotype presentations, in preparation for the meeting.

Before the group meeting, panelists rated the appropriateness of mutation testing, the level of disease severity, and whether they would consider medical therapy to be appropriate for a total of 217 scenarios. Ratings were completed independently by panelists. At the meeting (held by video conference in November 2020 because of the ongoing Coronavirus disease of 2019 pandemic), we discussed each item on which there was disagreement in the first round. Following this discussion, we clarified some items, added several scenarios, and removed others because they were unlikely to exist in the real world, leaving 127 scenarios to be rated by each panelist in the second round.

Items were rated on a 1–9 scale. The median rating was calculated for each item and categorized into 3 groups (1–3, 4–6, 7–9). Items with ≥2 individual ratings outside the category in which the median rating fell were defined as having a disagreement. For example, ratings of 4, 5, 6, 6, 7, 8, 8, 8, 8, 8, 9, 9, 9 would result in a median of 8 with disagreement because 4 ratings were outside the 7–9 range. Using these classifications, we analyzed patterns of agreement and disagreement and identified examples of clinical presentations of PROS that were mild (ratings 1–3), moderate (ratings 4–6), or severe (ratings 7–9) as well as circumstances when it would be inappropriate (ratings 1–3), appropriate (ratings 7–9), or uncertain (ratings 4–6) to test for mutation or consider providing medical therapy.

Results

Severity classification

The panel endorsed a disease severity framework defined by functional impairment, a reduction in quality of life, and risk

Table 1.

Severity Classification Framework

	Mildly Affected	Moderately Affected	Severely Affected
Functional impairments*	In adults: Some impact on instrumental activities of daily living (iADLs)†, eg, 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)‡ without supervision or assistance.	In adults: Cannot carry out iADLs, eg, does not use phone, unable to shop, needs to have meals prepared and served, does not travel. Some impact on ADLs, eg, needs help with bathing, dressing, cleaning self, and 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 adults: Cannot carry out iADLs or ADLs, eg, 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.
	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 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.	
Quality of life (QOL) reduction, eg, fatigue, depression/anxiety, pain, sleep disturbances	No or limited impact on QOL	Some reduction in QOL (eg, pain, depression/anxiety, fatigue that does not interrupt ADLs)	Significant reduction in QOL (eg, pain, depression/anxiety, fatigue that interrupts ADLs)
Risk of death	None	Increased risk of complications§ but not of death	Increased risk of death

*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).
†More complex activities required for independent functioning in community settings (eg, shopping, cooking, and managing finances).
‡Basic activities required for survival (eg, eating, bathing, and toileting).
§An unfavorable result of the disease.

Table 2.

Severity of Disease Grouped by Typical Clinical Findings

Impact of PROS		
Mild	**Moderate**	**Severe**
Isolated, well-circumscribed lymphatic malformation	Cutaneous lymphatic leakage	Paraspinal high flow or other high-risk lesion
Isolated (superficial) capillary-venous malformation	Bleeding that results in anemia and requires only oral iron support	Ascites or pleural effusion from lymphatic anomalies including chylothorax and chylous ascites (central conducting lymphatic abnormality)
Organ overgrowth without impaired function (eg, splenic enlargement without hypersplenism)	Bleeding that does not require intervention (eg, oral iron support or blood transfusion)	Inflammatory flare-ups and/or infections resulting in hospitalization
Musculoskeletal overgrowth not requiring surgical intervention with either no evidence of or nonprogressive scoliosis	Organ overgrowth with impaired function (eg, splenic enlargement with hypersplenism)	Thoracic and/or central phlebectasia*
Skin abnormalities (such as dermal melanocytic nevi, café-au-lait macules, hypopigmented macules, cutis marmorata, pigmented nevi, patchy hyperpigmentation that follows the lines of Blaschko, or linear keratinocytic epidermal nevi) with no impact on function, quality of life, or risk of death	Musculoskeletal overgrowth either not requiring surgical intervention with progressive scoliosis or requiring surgical intervention with either no evidence of or nonprogressive scoliosis	History of deep vein thrombosis or pulmonary embolism
	Contracture or joint involvement causing anatomic impairment that has some impact on ADLs	Increased risk of embolism due to a malformation with connection to deep venous system (ie, large, ectatic, or anomalous)
	Megalencephaly and/or neuronal migration defects (eg, may be due to brain overgrowth)	Bleeding that is life-threatening or requires blood transfusion
	Growth dysregulation (eg, failure to thrive, growth retardation, overgrowth in combination with undergrowth)	Compromised airway (eg, due to overgrowth or lymphatic malformation)
		Disordered aerodigestive function resulting from the nervous system or muscular involvement (eg, hypotonia, neuropathy)
		Disordered gross motor function (eg, needs help with bathing, dressing, feeding, some limits to mobility that can be compensated) resulting from musculoskeletal involvement (eg, overgrowth or progressive scoliosis)
		Intractable seizures despite medication (eg, may be due to brain overgrowth)
		Hypoglycemia with significant sequelae (eg, seizures)
		Visible distortion of anatomical landmarks causing disfigurement
		Intellectual disability that interrupts ADLs (eg, cannot manage basic physical needs, requires constant supervision)
		Severe pain that interrupts ADLs
		Disease-related malignancy (eg, Wilms tumor, teratoma)

The table presents examples of clinical findings that the panel agreed could classify patients as being mildly, moderately, or severely impacted by PROS. This is not a complete list and is intended to provide context to the circumstances we describe above for when mutation testing or medical therapy is recommended.
*Isolated and simple congenital dilatation of the central or cervical veins associated with risk of pulmonary embolism (Alomari et al. J Thorac Cardiovasc Surg 2010).

of death (Table 1). Specifically, severe PROS is associated with significant functional impairments (defined as an inability to carry out activities of daily living [ADL] or instrumental activities of daily living [iADL] in adults, and the need for constant supervision due to gross impairment in children), significant reduction in quality of life (eg, pain, depression/anxiety, fatigue that interrupts ADLs), and an increased risk of death. Clinical examples of severe presentations are shown in Table 2.

Similarly, moderate PROS is associated with some functional impairments (defined as an inability to carry out iADLs and some impact on ADLs in adults, some interference in social functioning, and the need for external support when sitting or mobility device when walking in children), some reduction in quality of life (eg, pain, depression/anxiety, fatigue that does not interrupt ADLs), and an increased risk of complications but not of death. The panel agreed that mild PROS is associated with minor functional impairments, no or limited impact on quality of life, and no increased risk of complications or death. Examples of moderate and mild presentations are shown in Table 2.

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 so, the panel agreed it is appropriate to test for a mutation in every moderately and severely affected patient. This would include when medical therapy with an mTOR, 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.

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. The panel was uncertain about the appropriateness of mutation testing in mildly affected patients when medical therapy with an mTOR inhibitor is being considered.

Medical management

In the second round, panelists agreed on 74% of ratings on medical therapy. Panelists agreed it may be appropriate to consider an mTOR inhibitor in some severely affected patients, regardless of age, whether a mutation is confirmed, or whether the disease is progressive or nonprogressive. They agreed it is appropriate to consider treatment with an mTOR inhibitor in some moderately affected children (3–12 years old) and adolescents/adults (>12 years old) with the disease that progresses over a 6-month interval, regardless of whether a mutation is confirmed or not. They agreed that mTOR inhibitor treatment was not appropriate in mildly affected patients with nonprogressive disease.

At the time this Delphi panel convened (2020), clinical trials had only recently begun, evidence was still limited, and 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* variant, or in those without a confirmed variant but with progressive disease. It may also be appropriate to consider PI3K or AKT inhibitors in severely affected infants (≤2 years old) with a confirmed mutation and progressive disease. In April 2022 (after this Delphi panel convened), the Food and Drug Administration approved the use of alpelisib, a PI3K inhibitor, for the treatment of adult and pediatric patients ≥2 years old with severe manifestations of PROS who require systemic therapy. The panel did not come to a consensus on the use of a PI3K or AKT inhibitor in mildly or moderately affected patients.

Discussion

Patients with PROS require complex management from a multidisciplinary team that may include dermatologists, geneticists, hematologists, oncologists, interventional radiologists, neurologists, and surgical specialists such as orthopedic surgeons, otolaryngologists, and plastic surgeons. At the time this panel convened, current treatments were not used with curative intent, rather they were partially therapeutic or provided on compassionate grounds. There was a variable body of evidence on the efficacy of mTOR, PI3K, or AKT inhibitors in PROS.[11–17] In April 2022, the Food and Drug Administration granted accelerated approval for the use of alpelisib in adult and pediatric patients ≥2 years old with severe manifestations of PROS who require systemic therapy.[18] However, unleashing these therapies' full potential in PROS will require selective treatment, dose/schedule optimization, rational combinations with other therapeutic approaches, and more clinical research.

The current panel recommended testing every moderately and severely affected patient except when the potential clinical harms outweigh the benefits or when costs make it unreasonable to do so. The panel also agreed it is appropriate to test for a mutation in mildly affected patients 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. Although the panel did not discuss specific testing methods, recent publications have emphasized the importance of deep coverage, high-sensitivity next-generation sequencing, full gene sequencing, the use of broad and frequently updated gene panels, and careful specimen selection (in consultation with clinicians, genetic counselors, and laboratory personnel).[19,20] The 2013 NIH panel recommended the use of affected tissue (overgrown tissue, vascular malformation, or epidermal nevus) for mutation analysis due to the somatic nature of most variants.[21] In patients eligible for testing, Keppler-Noreuil et al.[22] and Kuentz et al.[19] suggested testing freshly obtained affected tissue samples, such as skin biopsy specimens or surgical specimens from debulking procedures in visually affected tissues, for the most accurate results. In the absence of clearly affected tissue, biopsies of apparently unaffected overlying areas of involvement and buccal swabs adjacent to affected areas may be used, albeit with the possibility of lower diagnostic yield, compared to submission of the affected tissue.

The supporting evidence for the various treatments considered by the panel differed. mTOR inhibitors have been tested in at least 4 clinical trials of patients with PROS disorders with vascular malformations.[13–16] Response rates have been found to be dependent on the underlying malformation and the phenotypic and genotypic profile. The main challenges of mTOR inhibitors are tolerability and the duration of the treatment at an optimal dosage, especially in children. Our

panel aligned with these findings, concluding it was appropriate to consider an mTOR inhibitor in severely affected patients and in moderately affected children (3–12 years old) and adolescents/adults (>12 years old) with progressive disease (regardless of whether a mutation is confirmed or not), but not in mildly affected patients.

On the other hand, the evidence on the use of PI3K and AKT inhibitors in PROS is more limited. One case series and 1 case study of PI3K inhibitors[11,17] and 1 case series of AKT inhibitors[12] in patients with PROS have been shown to reduce the size of vascular or fatty malformations, stabilize renal function, reduce bleeding, and improve quality of life. There are also several ongoing observational studies (1 cohort study[23] and 1 retrospective medical chart review[24]) on the use of PI3K inhibitors and 2 ongoing clinical trials[25,26] on the use of AKT inhibitors. As a result, our panel was less certain about the appropriateness of these therapies in PROS. The panel agreed it may be appropriate to consider treatment with a PI3K or AKT inhibitor in severely affected children or adolescents/adults with a confirmed *PIK3CA* variant, or in those without a confirmed variant but with progressive disease. It may also be appropriate to consider PI3K or AKT inhibitors in severely affected infants (≤2 years old) with a confirmed mutation and progressive disease. The group did not come to an agreement as to whether it was appropriate or inappropriate to consider treatment with a PI3K or AKT inhibitor in mildly or moderately affected patients.

We used a well-established method to arrive at areas of consensus, but our study had 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. We recommend a similar panel be reconvened to address scientific advances in the field on a periodic basis. Although all panelists had significant experience in the field and were drawn from a diversity of backgrounds and geographic regions, 13 people cannot represent the full experience of clinicians who work in this field. While the modified Delphi method does have reasonable reproducibility (in a similar range as some common tests),[27,28] different groups of experts would be likely to reach different conclusions, at least on some issues. Evidence of this can be seen in the discussion about how to refer to this group of disorders. Eight panelists preferred the name "PIK3CA-related spectrum disorders," 4 preferred "PIK3CA-related overgrowth spectrum (PROS)," and 1 preferred "PIK3CA-related disorder spectrum."

Conclusions

Despite limited evidence and some remaining conflicting opinions, our panel agreed on a severity framework for PROS and specific circumstances when mutation testing or targeted medical therapy should be considered. These recommendations, representing the consensus of experts informed by published literature and experience, are a valuable addition to clinical guidelines for a rare and under-researched spectrum of diseases. Future research should validate this guidance using clinical data. Once validated, we hope these recommendations will improve outcomes for patients with PROS.

References

1. Keppler-Noreuil KM, Rios JJ, Parker VER, et al. *PIK3CA* -related overgrowth spectrum (PROS): diagnostic and testing eligibility criteria, differential diagnosis, and evaluation. Am J Med Genet. 2015;167(2):287–295.
2. Freed D, Stevens E, Pevsner J. Somatic mosaicism in the human genome. Genes. 2014;5(4):1064–1094.
3. Kang HC, Baek ST, Song S, Gleeson JG. Clinical and genetic aspects of the segmental overgrowth spectrum due to somatic mutations in PIK3CA. J Pediatr. 2015;167(5):957–962.
4. Akgumus G, Chang F, Li MM. Overgrowth syndromes caused by somatic variants in the phosphatidylinositol 3-kinase/akt/mammalian target of rapamycin pathway. J Mol Diagn. 2017;19(4):487–497.
5. Zhao L, Vogt PK. Helical domain and kinase domain mutations in p110 of phosphatidylinositol 3-kinase induce gain of function by different mechanisms. Proc Natl Acad Sci USA. 2008;105(7):2652–2657.
6. Dogruluk T, Tsang YH, Espitia M, et al. Identification of variant-specific functions of PIK3CA by rapid phenotyping of rare mutations. Cancer Res. 2015;75(24):5341–5354.
7. Bertino F, Braithwaite KA, Hawkins CM, et al. Congenital limb overgrowth syndromes associated with vascular anomalies. Radiographics. 2019;39(2):491–515.
8. Keppler-Noreuil KM, Parker VER, Darling TN, Martinez-Agosto JA. Somatic overgrowth disorders of the PI3K/AKT/mTOR pathway & therapeutic strategies. Am J Med Genet. 2016;172(4):402–421.
9. Madsen RR, Vanhaesebroeck B, Semple RK. Cancer-Associated PIK3CA mutations in overgrowth disorders. Trends Mol Med. 2018;24(10):856–870.
10. Novartis. FDA approves Novartis Piqray® - the first and only treatment specifically for patients with a PIK3CA mutation in HR+/HER2- advanced breast cancer. Published May 24, 2019. https://www.novartis.com/news/media-releases/fda-approves-novartis-piqray-first-and-only-treatment-specifically-patients-pik3ca-mutation-hrher2-advanced-breast-cancer
11. Venot Q, Blanc T, Rabia SH, et al. Targeted therapy in patients with PIK3CA-related overgrowth syndrome. Nature. 2018;558(7711):540–546.
12. Forde K, Resta N, Ranieri C, et al. Clinical experience with the AKT1 inhibitor miransertib in two children with PIK3CA-Related overgrowth syndrome. In Review; 2020.
13. Hammer J, Seront E, Duez S, et al. Sirolimus is efficacious in treatment for extensive and/or complex slow-flow vascular malformations: a monocentric prospective phase II study. Orphanet J Rare Dis. 2018;13(1):1–13.
14. Maruani A, Boccara O, Bessis D, et al.; Groupe de Recherche de la Societé Française de Dermatologie Pédiatrique. Treatment of voluminous and complicated superficial slow-flow vascular malformations with sirolimus (PERFORMUS): protocol for a multicenter phase 2 trial with a randomized observational-phase design. Trials. 2018;19(1):340.
15. Adams DM, Trenor CC, Hammill AM, et al. Efficacy and safety of sirolimus in the treatment of complicated vascular anomalies. Pediatrics. 2016;137(2):e20153257–e20153257.
16. Parker VER, Keppler-Noreuil KM, Faivre L, et al. Safety and efficacy of low-dose sirolimus in the PIK3CA-related overgrowth spectrum. Genet Med. 2019;21(5):1189–1198.
17. López Gutiérrez JC, Lizarraga R, Delgado C, et al. Alpelisib treatment for genital vascular malformation in a patient with congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and spinal/skeletal anomalies and/or Scoliosis (CLOVES) Syndrome. J Pediatr Adolesc Gynecol. 2019;32(6):648–650.
18. Research C for DE and. FDA approves alpelisib for PIK3CA-related overgrowth spectrum. FDA. Published online April 6, 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-alpelisib-pik3ca-related-overgrowth-spectrum. Accessed July 6, 2022.
19. Kuentz P, St-Onge J, Duffourd Y, et al. Molecular diagnosis of PIK3CA-related overgrowth spectrum (PROS) in 162 patients and recommendations for genetic testing. Genet Med. 2017;19(9):989–997.
20. McNulty SN, Evenson MJ, Corliss MM, et al. Diagnostic utility of next-generation sequencing for disorders of somatic mosaicism: a five-year cumulative cohort. Am J Hum Genet. 2019;105(4):734–746.
21. Chang F, Liu L, Fang E, et al. Molecular diagnosis of mosaic overgrowth syndromes using a custom-designed next-generation sequencing panel. J Mol Diagn. 2017;19(4):613–624.
22. Keppler-Noreuil KM, Sapp JC, Lindhurst MJ, et al. Clinical delineation and natural history of the *PIK3CA* -related overgrowth spectrum. Am J Med Genet. 2014;164(7):1713–1733.
23. Novartis Pharmaceuticals. Managed Access Program (MAP) to Provide Alpelisib (BYL719) for Patients With PIK3CA-Related Overgrowth Spectrum (PROS). clinicaltrials.gov. 2020. https://clinicaltrials.gov/ct2/show/NCT04085653. Accessed July 1, 2020.

24. Novartis Pharmaceuticals. Retrospective Chart Review Study of Patients With PIK3CA-Related Overgrowth Spectrum (PROS) Who Have Received Alpelisib as Part of a Compassionate Use Program (EPIK-P1). clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT04285723
25. Study of ARQ 092 in Subjects With PIK3CA-related Overgrowth Spectrum and Proteus Syndrome (MOSAIC). Clinicaltrials.gov identifier: NCT03094832. Published July 16, 2020. https://clinicaltrials.gov/ct2/show/NCT03094832. Accessed June 26, 2020.
26. Expanded Access to Provide ARQ 092 for the Treatment of Overgrowth Diseases and/or Vascular Anomalies. ClinicalTrials.gov Identifier: NCT03317366. Published October 23, 2017. https://clinicaltrials.gov/ct2/show/NCT03317366. Accessed June 26, 2020.
27. Merrick NJ, Fink A, Park RE, et al. Derivation of clinical indications for carotid endarterectomy by an expert panel. Am J Public Health. 1987;77(2):187–190.
28. Shekelle PG, Kahan JP, Bernstein SJ, Leape LL, Kamberg CJ, Park RE. The reproducibility of a method to identify the overuse and underuse of medical procedures. N Engl J Med. 1998;338(26):1888–1895.