NEWSLETTER

Genetic Overgrowth PI3K Support
www.gopi3ks.com

December 2018

Welcome to the newsletter for GoPI3Ks – Genetic Overgrowth PI3K Support. Here we will keep you informed of the current research, fundraising and stories from overgrowth patients.

An update from the Semple Lab

By Ralitsa Madsen, research fellow with Prof Robert Semple

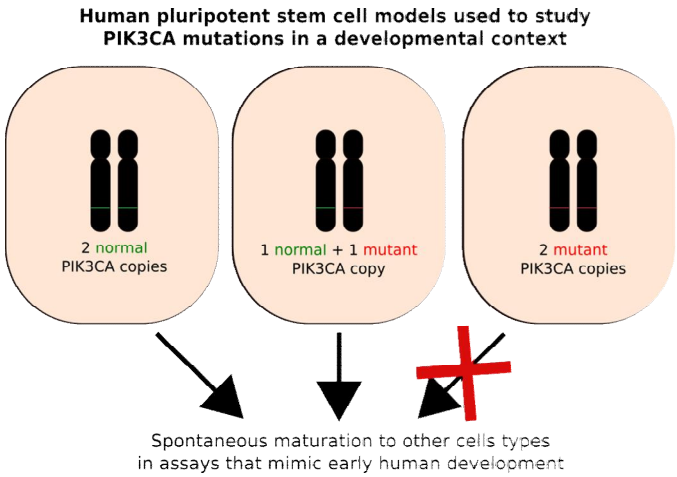
The Lab has seen a lot of change over the past year. We are now part of the University of Edinburgh and are still completing the set-up of all our equipment and procedures. The *PIK3CA* research has already picked up where it was left in Cambridge, however, and I will use this piece to give you some insight into the "basic" science that has been taking place as well as a sneak peek into what is yet to come.

I know that many of you get PROS updates from social media channels and may have come across a scientific review article on PROS, written by myself, Prof Semple and Prof Vanhaesebroeck in London earlier this year. When stripped of scientific jargon, it simply states what we know about the mechanisms that cause PROS and explains our view of the most important questions still to be answered. First, we know little about the role played by the *PIK3CA* gene in early human development, which is the time when a cell in the developing embryo acquires the *PIK3CA* gene change that causes PROS. Understanding this won't immediately point to a new treatment, but it will hold the key to understanding the patterns of abnormal growth seen in PROS as well as teaching us about the regulation of human development. Second, better "cell models" of PROS (that is, ways of studying PROS cells and tissues in a dish in the lab) are needed, ideally representing the full range of tissues that may be affected. As well as helping us to

understand how the abnormal growth occurs, such models may also be useful in testing proposed treatments such as Alpelisib and Taselisib.

With this in mind, the aim of my own research in Prof Semple's group over the past 3 years was to create *PIK3CA* changes seen in PROS in human cells which can turn into any other cell type in the human body. Cells with this ability are known as pluripotent stem cells. One way of making them is to start from skin biopsies from people with PROS. This involves treating cells with a combination of chemicals that "winds" the development of the cell backwards to an immature state similar to that seen in early embryos. It is also possible to use molecular scissors known as CRISPR to cut the genetic material of these cells either to introduce or to correct the PIK3CA gene change.

With help from Rachel Knox, whom many of you may know, I have used this approach to generate stem cells that either have two normal PIK3CA gene copies, one normal and one changed/mutant copy (as is the case in PROS), or two changed/mutant copies (we didn't even know before that this was possible!). A key discovery has been that cells with two abnormal copies PIK3CA behave very differently to normal cells and to cells with only have one copy of the change (see diagram). When development of these cells was studied, either in a dish or in mice, the presence of two changed copies blocked the cells from maturing into other cell types. These observations suggest that a human embryo with two copies of the abnormal PIK3CA would fail to develop beyond the second week of pregnancy.



We were surprised that the cells with one abnormal copy of PIK3CA behaved similarly to normal cells in most tests, especially as this is the situation in PROS. This shows that the problem in PROS is more likely related to problems at later stages of development, and/or to small changes in the way tissues grow. Although these changes are small, their effects mount up with time to cause the problems

seen in PROS. We now need to study some of the cells that appear later in development including fat cells or the cells lining blood vessels, which are commonly affected in PROS. This is something that we plan to do in the near future.

My current efforts are focussed on using a range of cutting edge techniques to make the stem cells even more useful for studying PROS. This includes labelling cells with a molecular "identity tag", which will allow me to create mixtures of normal and abnormal cells. We believe that these will be better models of PROS where normal and mutant cells typically live side-by-side in the overgrown tissue. Once established, we hope to use this new system for testing potential new medicines and to dig further into the mechanisms causing PROS. We are hopeful that there will be more to report in a year's time, so stay tuned! In the meantime, a very merry Christmas and a happy new year from the Semple group.

FUNDRAISING

Over this year there has been some amazing fundraising events that have taken place to raise funds for GoPI3Ks. **A BIG THANK YOU** to everyone who has helped, you have really made a difference.

In 2017 I was contacted by Samantha Barnes who had taken part in a 10K run with all proceeds going to GoPI3Ks. A huge thank you to Samantha who raised an amazing £550. Here is Samantha's story.

My son, Thomas age 20 months, is diagnosed with pik3ca overgrowth. He has a large foot and leg on the right side. It doesn't bother him at all of course!

Whilst trying to struggle fitting all his hospital appointments around work, things got to me a bit so I decided to do something positive.

I used to do a bit of jogging before having Thomas, so I decided to do the Wigan 10km in September 2017 and try to beat my time of the last one I did about 6 years previous.

We put the sponsorship form up at work, and everyone was very generous. And I managed 1 hour 4 minutes, not a great time, but the best I have ever done

In 2017 we applied to Pendle Powerfest: https://www.pendlepowerfest.com/about-us for some funding, to our surprise they made us their Community Champion for 2018. This meant we could go along to all their events & raise awareness & funds for GoPI3Ks.

We attended their car event at Burnley Football Club in April 2018 – we sold homemade cakes & gave out information to anyone who would like to know what GoPI3Ks is & what we do. Despite the yucky rain & wind, there was a good turnout & we made £85.


In May we joined the Pendle Powerfest guys again, this time at their main show, we battled with the wind (chasing after run away tombla tickets) to make sure we could get our tombola up & running, we also had our homemade cakes for sale. Plus a chance of winning a £50 experience day voucher by guessing the mystery car in the envelope.

We had a fun day & it was good to see such a great turnout plus great to see such support from family, friends as well as the organisers of the event. We managed to raise £221.30


One night in early September I received a phone call from the committee at Pendle Powerfest, We have some news for you (what could this be?) After careful consideration they felt that our commitment over the year to attend their events, raise the profile of GoPI3Ks & raise much needed funds, these wonderful people wanted to give us a little more money than we initially expected. This amazing amount went a long way to paying for the first ever GoPI3Ks weekend.

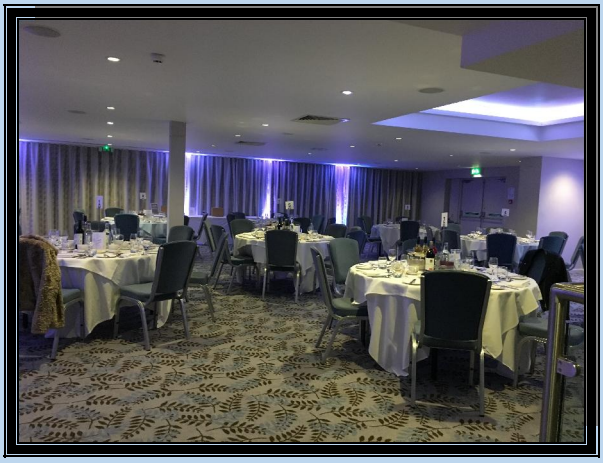
****DRUM ROLL PLEASE****

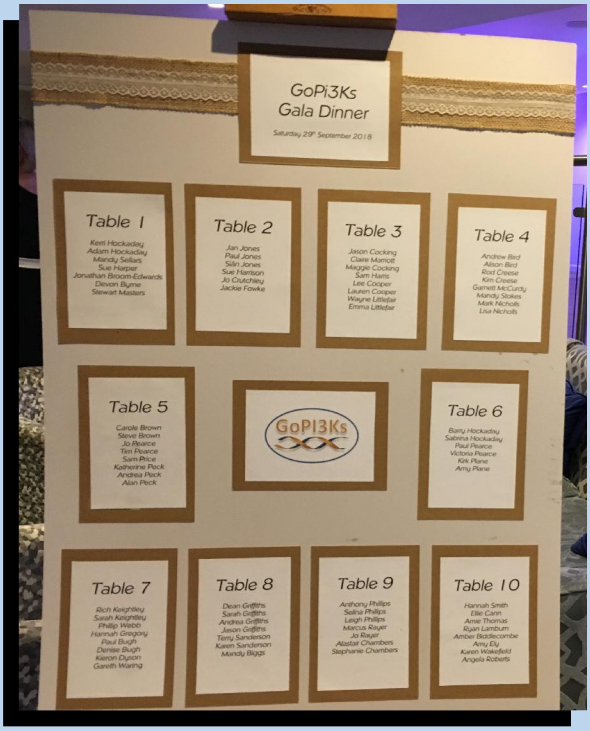
After tea & biscuits our committee members (myself (Mandy) Yvonne & Sue were presented with this HUGE (in more ways than one) cheque.

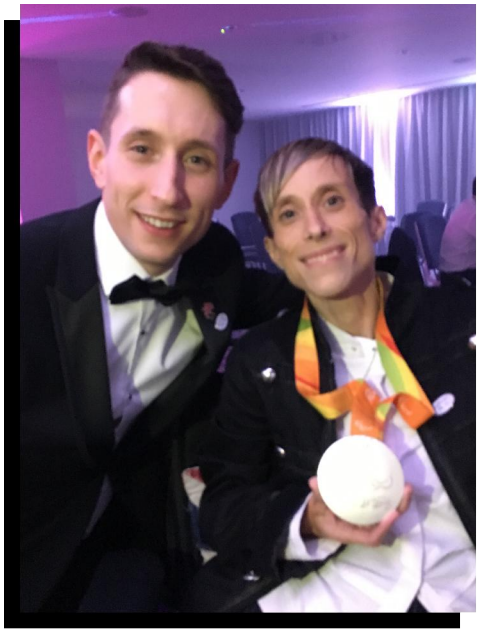
One of our GoPI3Ks families, Kerri & Adam Hockaday wanted to raise funds for GoPI3Ks, so this is where the first ever GoPI3Ks Gala Dinner was born. The evening was wonderfully organised, with a devine 3 course evening meal, raffle, photo booth, comedian & last but not least, Paraymplian Jonathan Broom-Edwards as our very inspriational guest speaker.

What a magical evening & Jonathan's speech was truly inspiring, everyone had a lot of fun & gave generously, the total raised on the evening was a wonderful £500.

We are hoping to be able to make this an annual event with interest from potential sponsors who attended the evening.







A **HUGE THANK YOU** to Joan Oliver for spending time organising a raffle & managing to raise £235 for GoPI3Ks

THANK YOU

A **BIG THANK YOU** also goes to Mr & Mrs Reid, the family of Mandy Powell (a GoPI3Ks member) who instead of asking for presents for the big 80, people donated raffle prizes & the money was given to GoPI3Ks

How GoPI3Ks have helped people this year

Earlier in the year we were contacted by James Vincent who due to PROS needs his clothes adapting to fit. GoPI3Ks was more than happy to pay for these.

One of our goals when setting up this charity was to give members support & also provide, where possible, information on research & current medical treatments. The best way we could provide this would be by organising a family weekend where our members came together with leading doctors who would give presentations. On 27th October 2018 our first GoPI3Ks family weekend took place in London, with great success.

GOPI3KS FAMILY WEEKEND

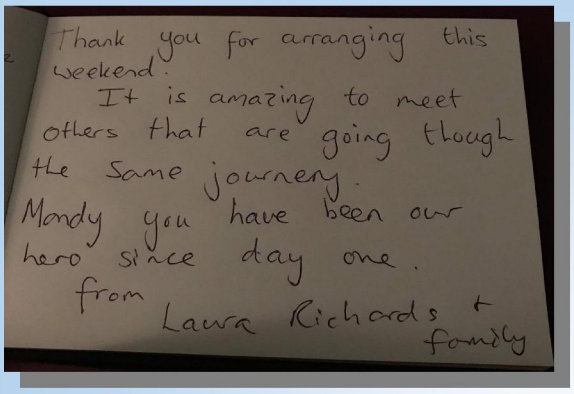
On Saturday 27th of October we held our first GoPI3Ks family weekend along with the Proteus Syndrome Foundation (PSF)

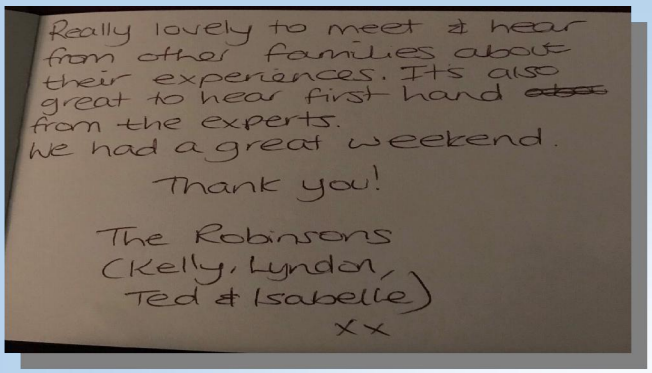
For many GoPI3Ks members, this would be the first time that many parents and children alike would have met anyone with the same condition. We are all very aware of how isolating it can feel to not have that psychological support or knowledge of what can happen to you or your child as they get older.

This weekend was the perfect opportunity for families & patients to get to know each other & listen to each other experiences plus to also have the opportunity to listen to the leading doctors in the field speak about recent research & possible treatments.

Kate Bod
Yesterday at 22:48 ·

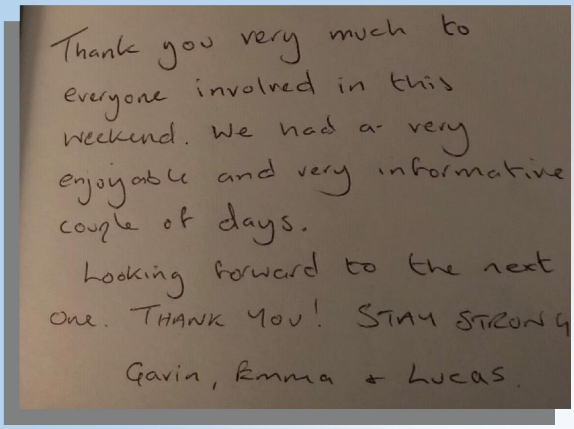
Would also like to send out a huge thank you to Mandy for the weekend. Really special to make new friends, and to have time with such great and inspiring people. These photos from the photo booth sums up the experience for usually shy and retiring daughter Meg who often says she feels she doesn't fit in due to "being different". She was on a high all weekend, she loved the children she met, and was so happy that she was finally meeting others with her condition, it meant the world to her. Thank you Mandy, the doctors, the speakers, the wonderful ladies who looked after the kiddies, and everyone else behind the scenes too for making it all possible. Wow 🌟





Kelly Pearce
Yesterday at 12:20 ·

It's been really lovely to meet you all! I hope you all get home safely and look forward to seeing you again sometime in the future 😊 thanks again **Mandy Sellars** for doing a great job for us all xx



After a day of listening to doctors presentations, it was time for the families to let their hair down with our photo booth.

What the first GoPI3Ks family weekend meant to one of our members:

I was nervous going along to the PIK3CA weekend, with daughters Meggie aged 10 & Sophia aged 9 in tow (Meggie has PIK3CA, she has had a leg shortening procedure that didn't work & is awaiting her next surgery for leg lengthening). We needn't have been worried. Everyone was so friendly, with big smiles and greetings from the moment we arrived. The weekend was so well organised. My girls loved the children's activities & didn't tire of them at all, spending hours with the lovely ladies who were so warm & fun, & orchestrated all sorts of fun distractions including films, bubbles, slime making, pumpkin carving etc. This left us parents able to concentrate on the talks in another room. It was fascinating to learn about the latest research & findings, & to hear from leaders in the field in the UK and the US. So grateful to the doctors for taking such long journeys to the venue, giving up their time, & spending time with parents on one to one meetings. Found the advice priceless.

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As a family we'd been feeling very isolated in the pik3ca world. My daughter often said that she wished she could meet someone with the same condition. We met the most wonderful people also with PIK3CA on the weekend & it has changed everything for us. It was extraordinary to chat with others in the same boat, to compare notes on doctors, treatments, experiences. To find that we weren't alone with that feeling of isolation, of feeling unsupported by the medical community. So often over the years we had seen doctors who would simply say that they didn't know anything about the condition and couldn't help. It seemed that we all had this in common

I also found it very interesting to discover that siblings of those with PIK3CA were also struggling in their own way due to the time & attention that is devoted to their brother/sister. The weekend was transformational for our family & I can't thank Mandy enough. If she hadn't set up her Gopik3ca FB page, & hadn't organised this weekend, we would still be feeling alone with what can be an immense struggle with all sorts of ramifications for families involved on the journey. We made some wonderful friends on the weekend, who I know we'll stay in touch with. I remember looking around the room on the quiz night & it was really special to see everyone having fun together, to see previously tense faces relaxed in laughter and companionship. When we returned home after the conference there was a letter waiting for us on the mat announcing Meggie's next operation date. For once I didn't feel overwhelmed, I felt that we had the strength to face it & that everything would be OK. We no longer feel alone in the battle or on the journey… thank you Mandy.

We were lucky enough to have Professor Rob Semple attend our family weekend. He is leading the way on PIK3CA research & treatment in the UK.

Update on UK PIK3CA Overgrowth Research

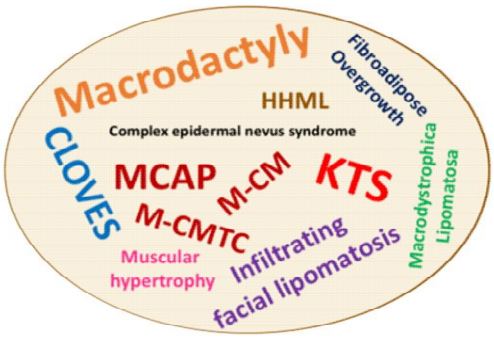
October 2018

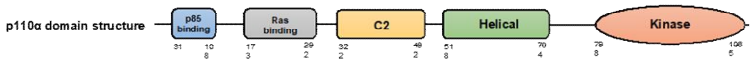
Robert Semple

rsemple@ed.ac.uk

PIK3CA-Related Overgrowth Spectrum

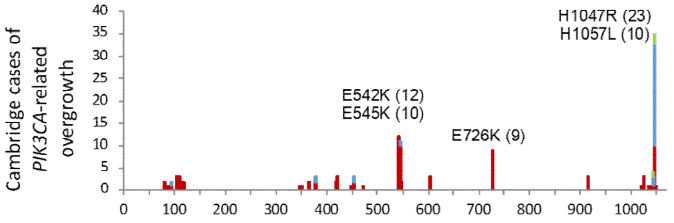
2018 *vs* 2012



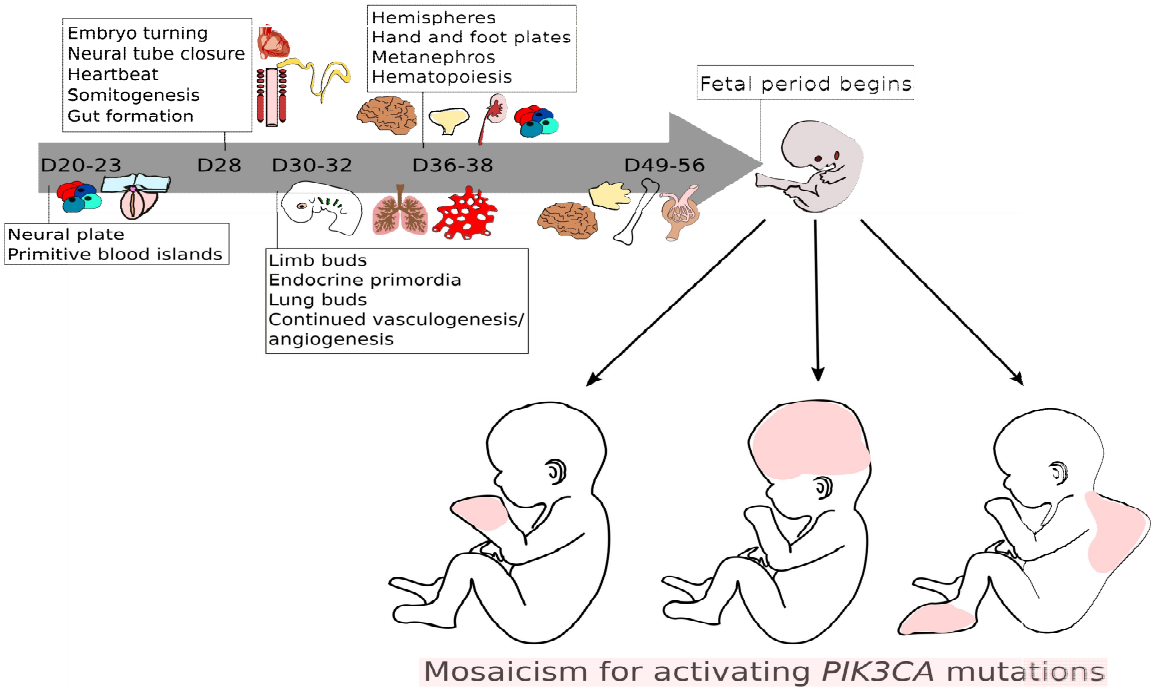


SOS Segmental Overgrowth Study

120 diagnosed *PIK3CA* mutations (13 September 2016)



"Mosaic" *PIK3CA mutations from early development*



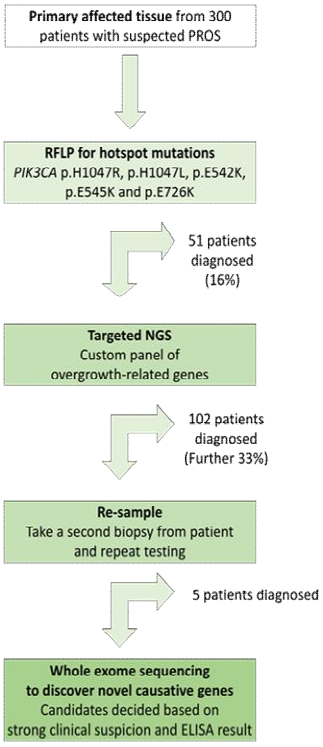
Aim: To minimize adverse effects of PROS on the lives of patients and families

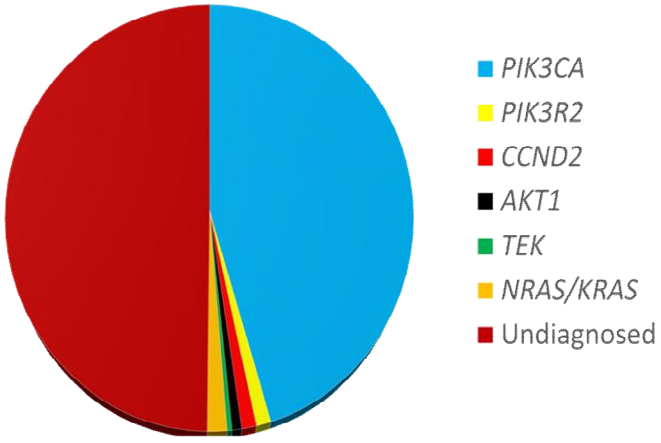
How?

- Earlier accurate diagnosis
- Informed, personalised advice
- Good social/personal support
- The right treatments at the right time
- Better treatments

Earlier recognition and accurate diagnosis
Informed, personalized advice

- Many 100s of people (probably 1000s) with PROS now known
- Growing numbers of case series published





Challenges:

1. Best approach where genetic testing negative (how many biopsies/samples?)
2. Increasing awareness among doctors
3. Making sure testing available in the NHS

The right treatment(s) at the right time
(Biggest impact in the shortest time?)

Ensure advice from experienced multidisciplinary teams available to all, organized to minimize inconvenience/disruption from healthcare

- A problem of funding, service organization, and advertising
- Needs patient groups and doctors working together to make the case to those holding the purse strings

Better treatments

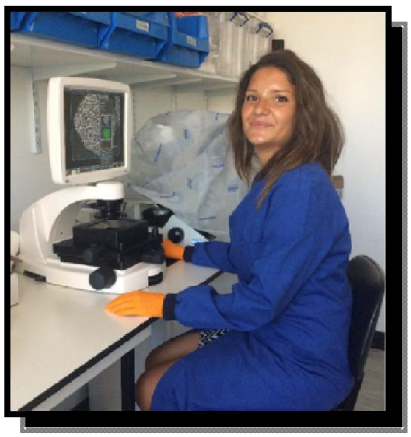
Improved scientific understanding of the development of PROS
(Fundamental scientific research: long term benefit)

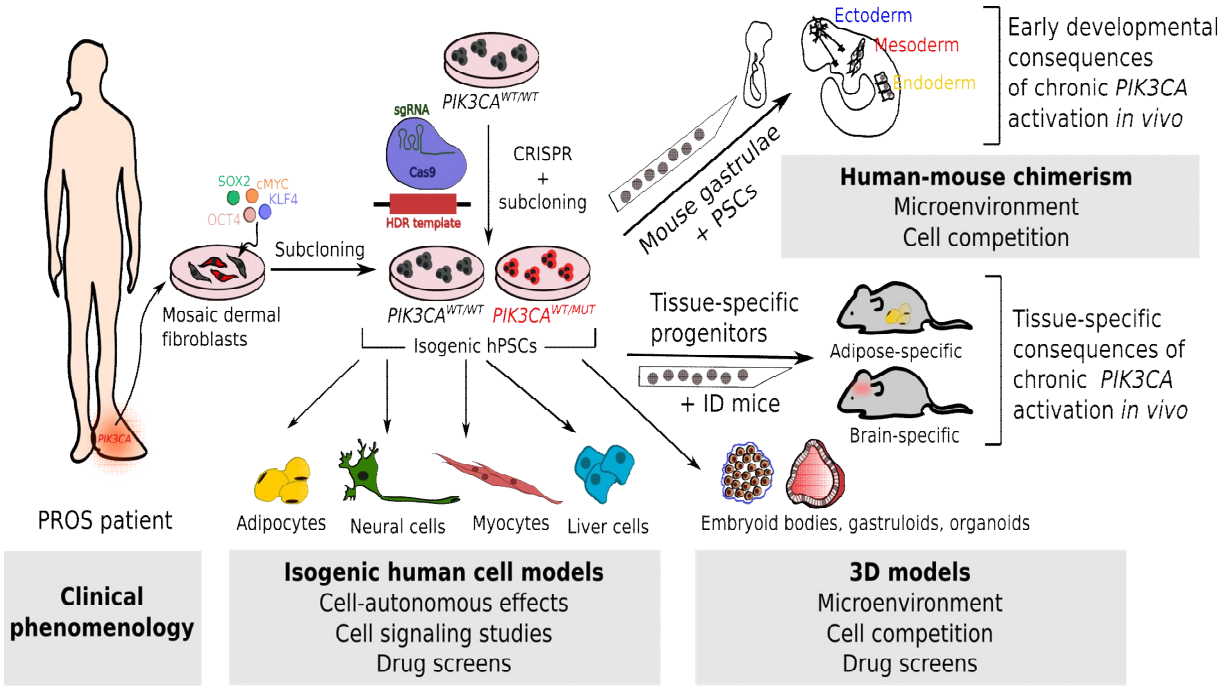
Assessment of medications already used for other conditions
(Drug "repurposing": short/medium term benefit)

Assessment of trial drugs not currently in clinical practice
(medium term benefit)

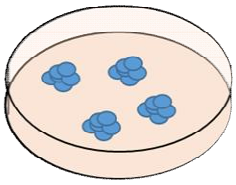
PARTNERSHIP AMONG DOCTORS/SCIENTISTS/PHARMACEUTICAL COMPANIES

"Basic" Science

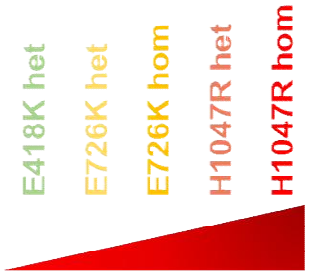




Disease modelling of PROS using engineered human iPSCs

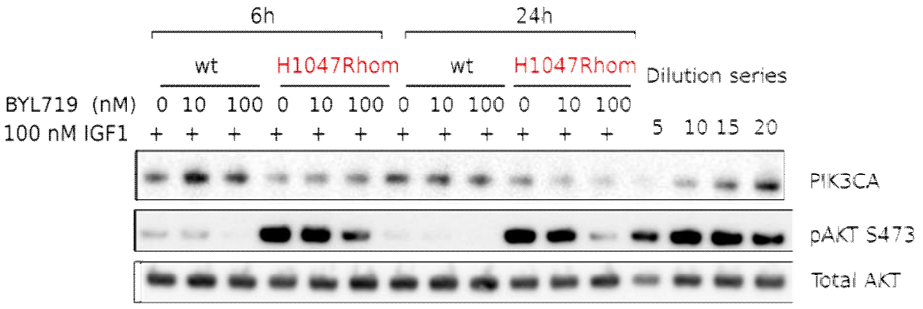


CRISPR/Cas9

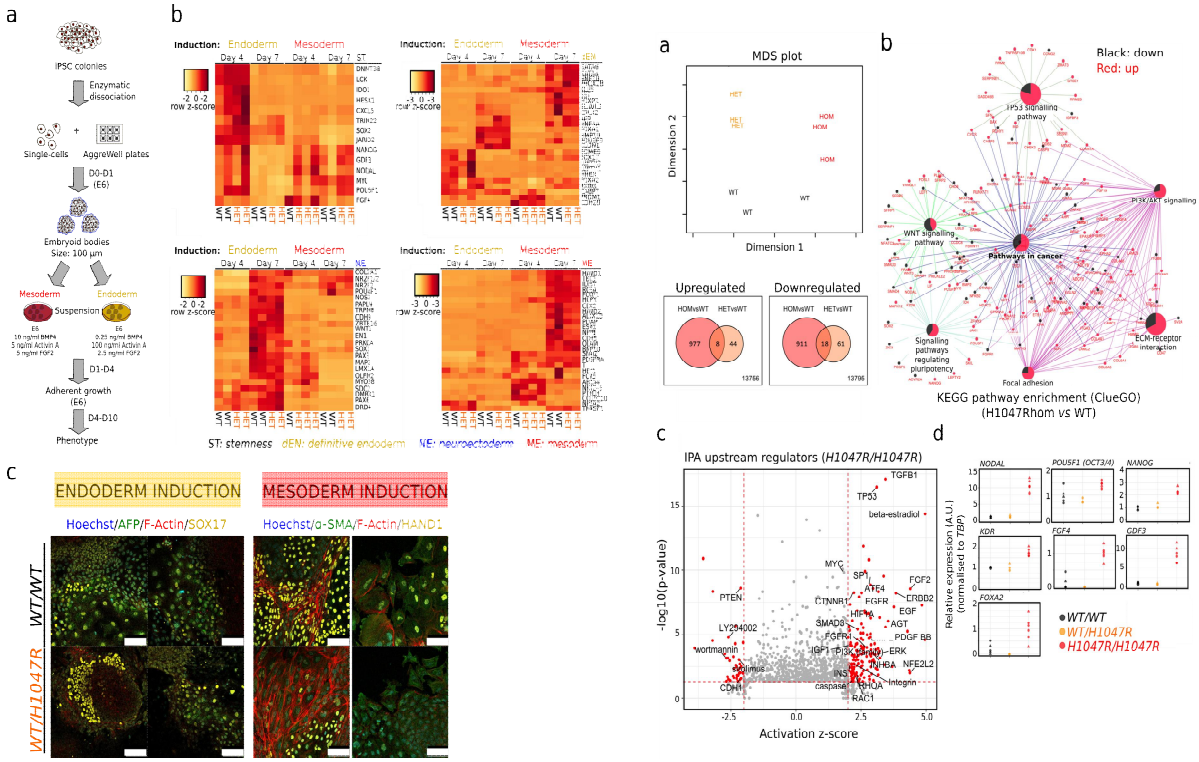


Graded allelic series of activating *PIK3CA* mutants

Ralitsa Madsen
Rachel Knox



Disease Modelling in Human Stem Cells



Critical Questions/Challenges for Trials

- Which PROS-related problems are reversible and which are determined before birth?
- What measurements can be made in such a variable condition allowing comparison across groups?
- How do we take into account normal growth?
- How do we deal with the common lack of safety studies in children for many emerging trial medicines?

Types of evidence for net benefit of new medicines

N.B. *Primum non nocere*/ Risk *vs* benefit!!

- Anecdotes
- Case reports and case series (sometimes from emergencies)
- Unblinded pilot studies
- Other trial designs
- Randomised, double blinded controlled trials

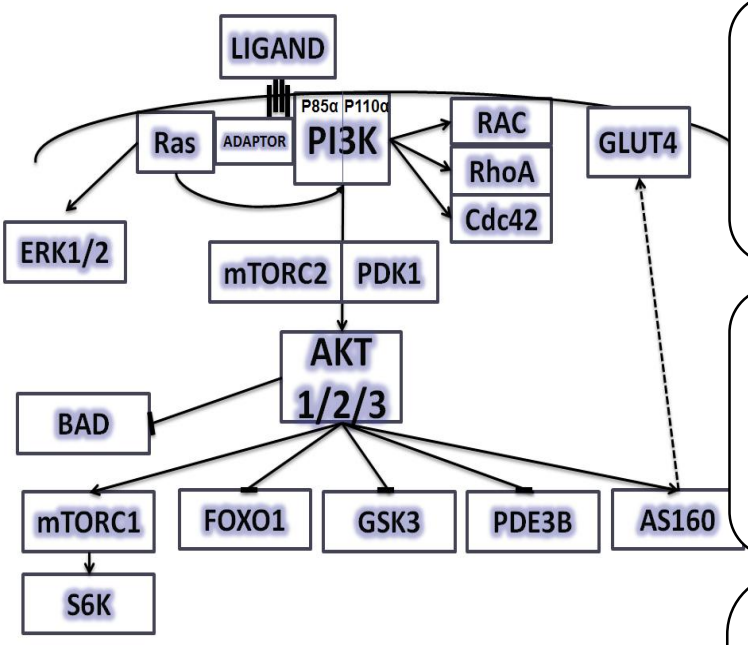
Key Factors to Consider in Trials of Experimental Drugs in Rare Diseases

- Will they hit the target you want to hit?
- Are they likely to be safe? What about children? (Have they been used before in people for other conditions?)
- What are the practicalities and costs of running the study (condition, geography etc) - What sort of study should be run?
- Is the company that owns the rights a willing partner? – Will they back the studies needed to prove a new treatment is of benefit?

Potential Therapies

mTORC1 inhibitors

- Available since 1990s
- Long-term use; established safety



PI3K/ p110α inhibitors

- Phase II – Cancer

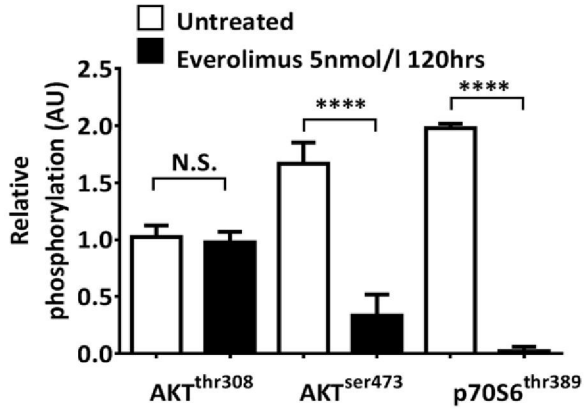
AKT inhibitors

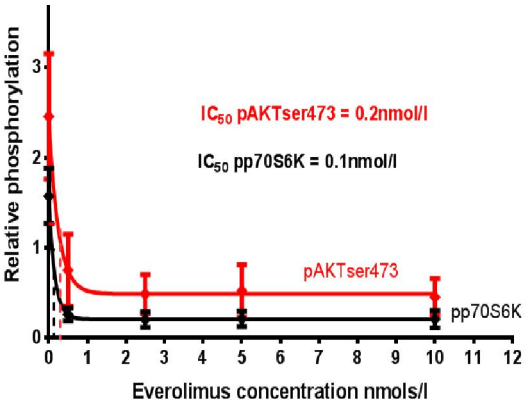
- Phase II/III –Cancer trials

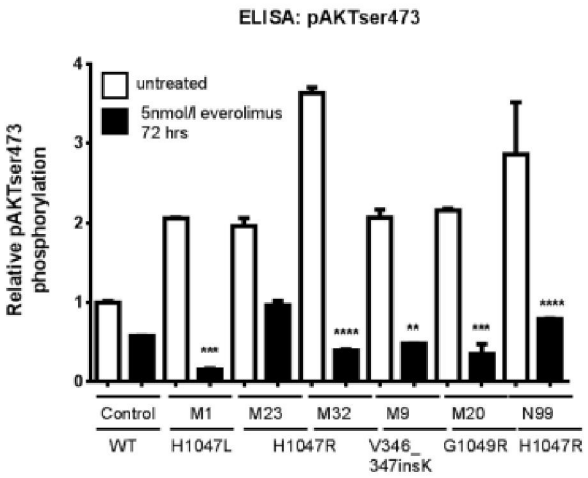
Dual inhibitors e.g. PI3K/AKT: PI3K/mTOR

- Phase II/III –Cancer trials

Effect of Everolimus on Hyperactivated Basal PI3K Signalling







PROMISE Study of sirolimus (Cambridge, NIH (Bethesda), Dijon)

- A “phase 2” pilot study
- Open label (doctors and patients know drug)
- 6 month pre treatment measurement; 6 months low dose sirolimus
- 3 independent, *identical*, studies run in parallel
- Primary Objective
  - To assess safety and calculate an approximate effect size of sirolimus therapy in PIK3CA-related overgrowth, to guide further study design

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ARTICLE | Genetics inMedicine

Safety and efficacy of low-dose sirolimus in the PIK3CA-related overgrowth spectrum

2018

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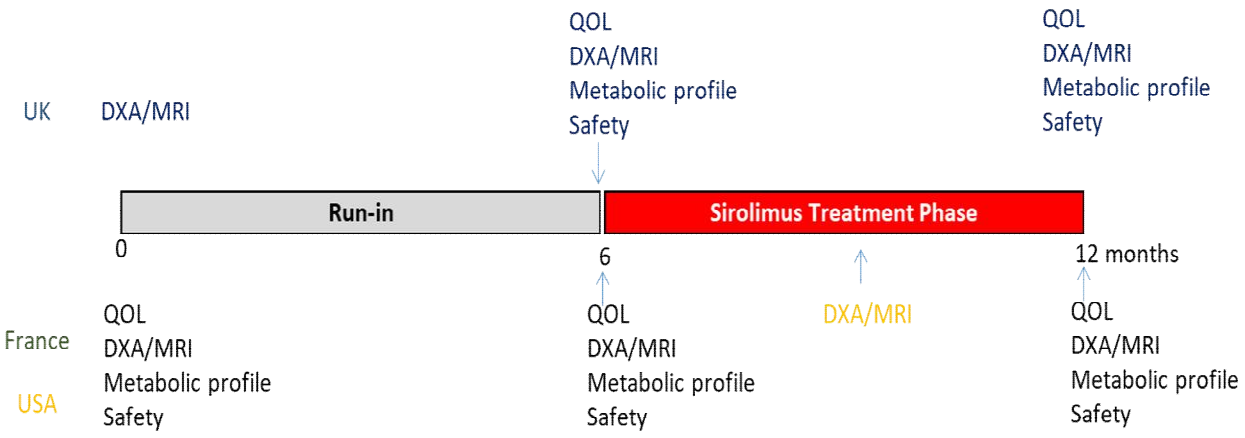
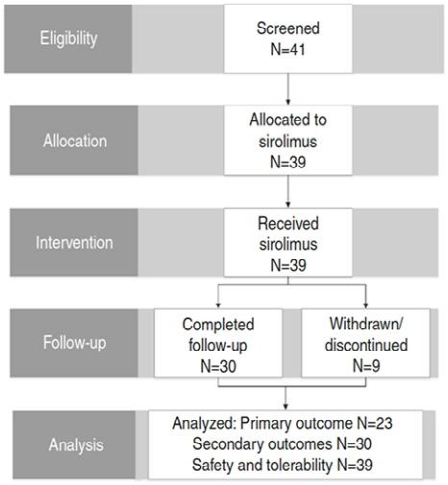
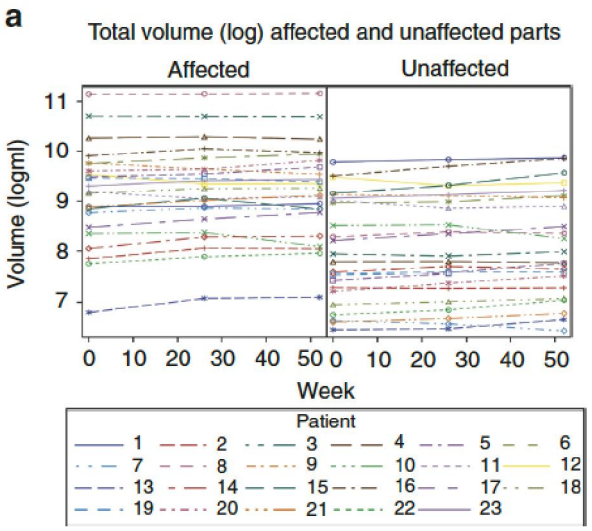
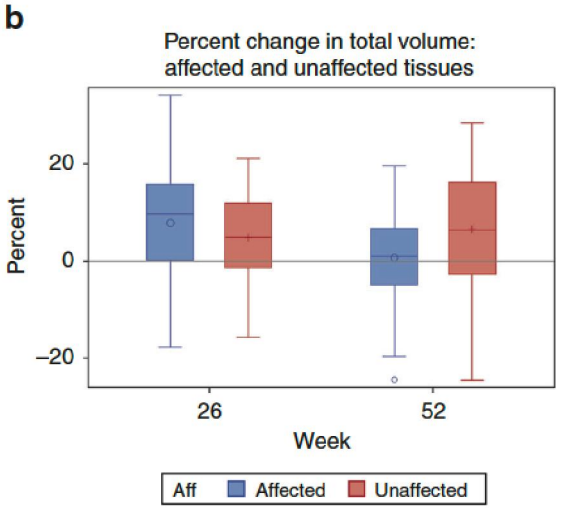
Overview of Study

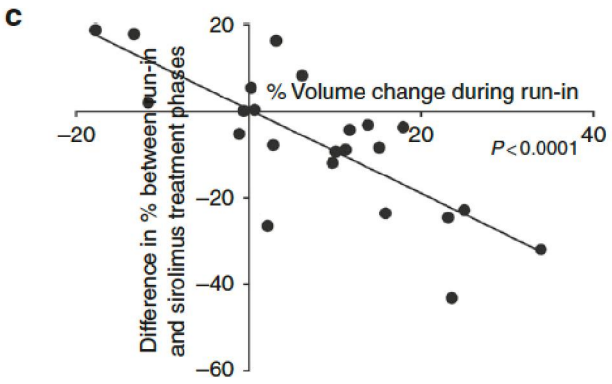




Primary Endpoint







For the primary outcome measure, a significant reduction of −7.2% (SD 16.0; $p = 0.04$) was observed in the volume change of affected tissues during sirolimus treatment. In contrast, there was no significant increase for unaffected tissue (+1.7%, SD 11.5; $p = 0.48$). A significant reduction in lean tissue (muscle, connective tissue, and vasculature) of −6.3% (SD 13.3; $p = 0.03$) and a trend toward reduction of fat of −9.8% (SD 24.4; $p = 0.07$) was observed at affected but not unaffected sites during treatment (Supplementary Table S4). Viewing individual data points on scatter plots comparing volume changes in treated and untreated phases reinforces this conclusion (Supplementary Figure S1).

But…. Significant Side Effects

Serious Adverse Events

Class	Description	CTCAE severity grade	Relatedness	Outcome	Led to Discontinuation of Sirolimus?
Blood and lymphatic disorders	Anemia	3	Not related	Hospitalization	No
	Anemia	2	Not related	Hospitalization	No
	Neutropenic fever	3	Not related	Clinically important	No
	Neutropenia	4	Possible	Clinically important	Yes
Gastrointestinal disorders	Constipation aggravated	3	Not related	Hospitalization	No
Infections and infestations	Appendicitis	3	Not related	Hospitalization	No
	Cellulitis of face	3	Possible	Hospitalization	No
	Cellulitis of foot	3	Possible	Hospitalization	Yes
	Epstein Barr Virus infection	3	Possible	Hospitalization	No
	Cellulitis	3	Possible	Hospitalization	No
	Cellulitis	3	Possible	Hospitalization	No
	Cellulitis	3	Possible	Hospitalization	No
	Cellulitis	3	Not related	Hospitalization	No
	Pelvic infection	3	Possible	Hospitalization	No
	Pneumonia	2	Not related	Hospitalization	No
	Viral meningitis	3	Possible	Hospitalization	No
Injury, poisoning and procedural complications	Over-medication	1	Definite	Clinically important	No
Musculoskeletal and connective tissue disorders	Sirolimus hypersensitivity syndrome	3	Definite	Hospitalization	Yes
Respiratory, thoracic and mediastinal disorders	Interstitial pneumonitis	3	Definite	Hospitalization	Yes
Vascular disorders	Hemarthrosis	2	Possible	Hospitalization	No
	Pulmonary embolus	3	Probable	Hospitalization	Yes

Class of AE	Grade	Possible	Probable	Definite	Total
Blood and lymphatic disorders	1	2/39 (5%)	0	0	
	2	1/39 (3%)	0	0	
	3	1/39 (3%)	0	0	
	4	1/39 (3%)	0	0	
					8/39 (21%)
Gastrointestinal disorders	1	2/39 (5%)	0	0	
					2/35 (6%)
Infections and infestations	1	7/39 (18%)	1/39 (3%)	0	
	2	8/39 (21%)	0	0	
	3	5/39 (13%)	0	0	
					16/39 (41%)
Injury, poisoning and procedural complications	1	0	0	1/39 (3%)	
					1/39 (3%)
Metabolism and nutrition disorders	1	0	0	3/39 (8%)	
					3/38 (8%)
Musculoskeletal and connective tissue disorders	3	1/39 (3%)	0	0	
					1/39 (3%)
Nervous system disorders	1	1/39 (3%)	0	1/39 (3%)	
					2/39 (5%)
Renal and urinary disorders	1	1/39 (3%)	0	0	
					1/39 (3%)
Respiratory, thoracic and mediastinal disorders	1	1/39 (3%)	0	0	
	3	0	0	1/39 (3%)	
					2/39 (5%)
Skin and subcutaneous disorders	1	2/39 (5%)	0	0	
					2/39 (5%)
Vascular disorders	1	1/39 (3%)			
	2	1/39 (3%)			
	3		1/39 (3%)		
					3/39 (8%)

Conclusions and Further Questions

Purpose: *PIK3CA*-related overgrowth spectrum (PROS) encompasses a range of debilitating conditions defined by asymmetric overgrowth caused by mosaic activating *PIK3CA* variants. *PIK3CA* encodes the p110α catalytic subunit of phosphatidylinositol-3-kinase (PI3K), a critical transducer of growth factor signaling. As mTOR mediates the growth-promoting actions of PI3K, we hypothesized that the mTOR inhibitor sirolimus would slow pathological overgrowth.

Methods: Thirty-nine participants with PROS and progressive overgrowth were enrolled into open-label studies across three centers, and results were pooled. For the primary outcome, tissue volumes at affected and unaffected sites were measured by dual energy X-ray absorptiometry during 26 weeks of untreated run-in and 26 weeks of sirolimus therapy.

Results: Thirty participants completed the study. Sirolimus led to a change in mean percentage total tissue volume of −7.2% (SD 16.0, $p = 0.04$) at affected sites, but not at unaffected sites (+1.7%, SD 11.5, $p = 0.48$) ($n = 23$ evaluable). Twenty-eight of 39 (72%) participants had ≥1 adverse event related to sirolimus of which 37% were grade 3 or 4 in severity and 7/39 (18%) participants were withdrawn consequently.

Conclusion: This study suggests that low-dose sirolimus can modestly reduce overgrowth, but cautions that the side-effect profile is significant, mandating individualized risk–benefit evaluations for sirolimus treatment in PROS.

Genetics in Medicine (2018) https://doi.org/10.1038/s41436-018-0297-9

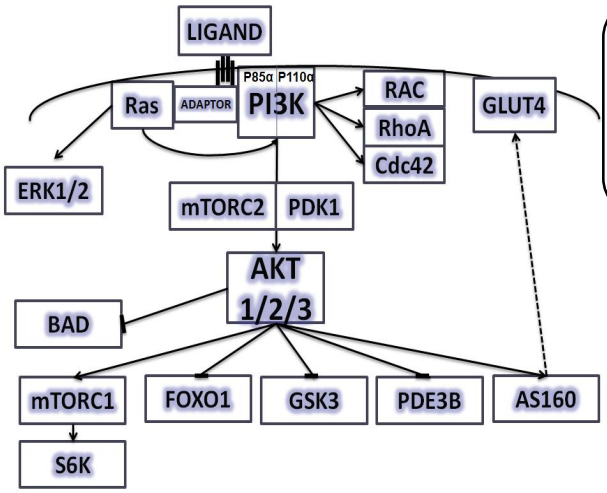
Keywords: overgrowth; mosaicism; *PIK3CA*; sirolimus

- Are particular features in PROS more likely to respond to sirolimus?
- Would a higher dose of sirolimus have a bigger effect?
- How many complications were due to sirolimus, and how many due to PROS itself?
- How should a more formal study now be designed to answer these questions?

Potential Therapies

mTORC1 inhibitors

- Available since 1990s
- Long-term use; established safety profile



PI3K/ p110α inhibitors

- Phase II – Cancer trials

AKT inhibitors

- Phase II/III – Cancer trials

Dual inhibitors e.g. PI3K/AKT: PI3K/mTOR

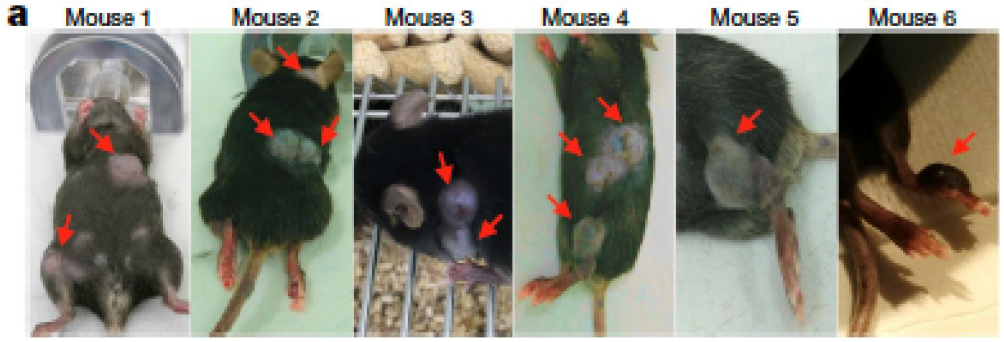
- Phase II/III – Cancer trials

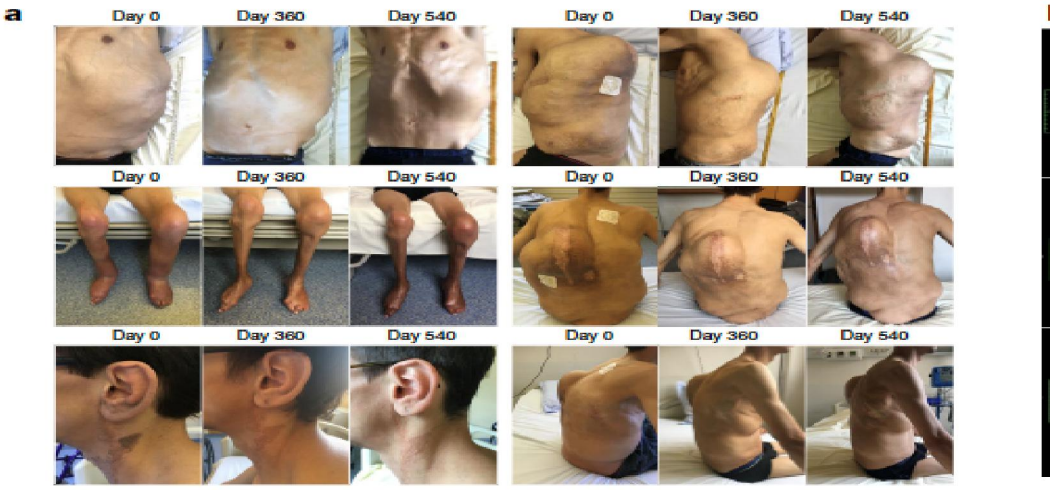
Alpelisib and PROS – Case series

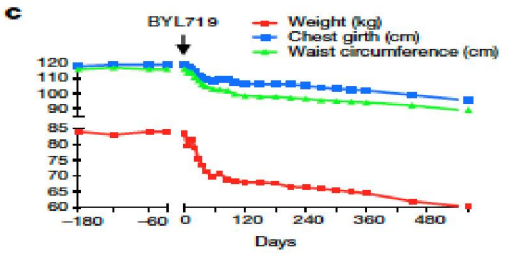
Targeted therapy in patients with PIK3CA-related overgrowth syndrome

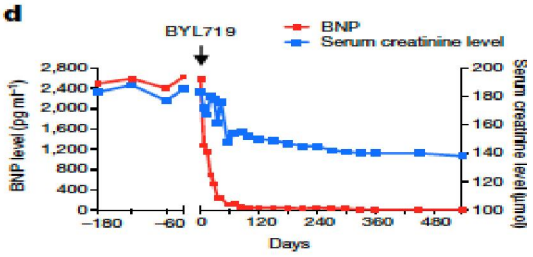
Quitterie Venot[1], Thomas Blanc[1,2,3,21], Smail Hadj Rabia[2,4,5,21], Laureline Berteloot[5,6], Sophia Ladraa[1], Jean-Paul Duong[2,7], Estelle Blanc[8], Simon C. Johnson[9], Clément Hoguin[1], Olivia Boccara[4], Sabine Sarnacki[2,3], Nathalie Boddaert[2,5,6], Stephanie Pannier[2,10], Frank Martinez[11], Sato Magassa[1], Junna Yamaguchi[1], Bertrand Knebelmann[1,2,11], Pierre Merville[12,13], Nicolas Grenier[14], Dominique Joly[1,2,11], Valérie Cormier-Daire[2,5,15], Caroline Michot[2,5,15], Christine Bole-Feysot[5], Arnaud Picard[2,16], Véronique Soupre[16], Stanislas Lyonnet[2,5,15], Jeremy Sadoine[17], Lotfi Slimani[17], Catherine Chaussain[2,17], Cécile Laroche-Raynaud[18], Laurent Guibaud[19], Christine Broissand[20], Jeanne Amiel[2,5,15], Christophe Legendre[1,2,11], Fabiola Terzi[1,2] & Guillaume Canaud[1,2,11]*

CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal syndrome) is a genetic disorder that results from somatic, mosaic gain-of-function mutations of the *PIK3CA* gene, and belongs to the spectrum of *PIK3CA*-related overgrowth syndromes (PROS). This rare condition has no specific treatment and a poor survival rate. Here, we describe a postnatal mouse model of PROS/CLOVES that partially recapitulates the human disease, and demonstrate the efficacy of BYL719, an inhibitor of PIK3CA, in preventing and improving organ dysfunction. On the basis of these results, we used BYL719 to treat nineteen patients with PROS. The drug improved the disease symptoms in all patients. Previously intractable vascular tumours became smaller, congestive heart failure was improved, hemihypertrophy was reduced, and scoliosis was attenuated. The treatment was not associated with any substantial side effects. In conclusion, this study provides the first direct evidence supporting PIK3CA inhibition as a promising therapeutic strategy in patients with PROS.





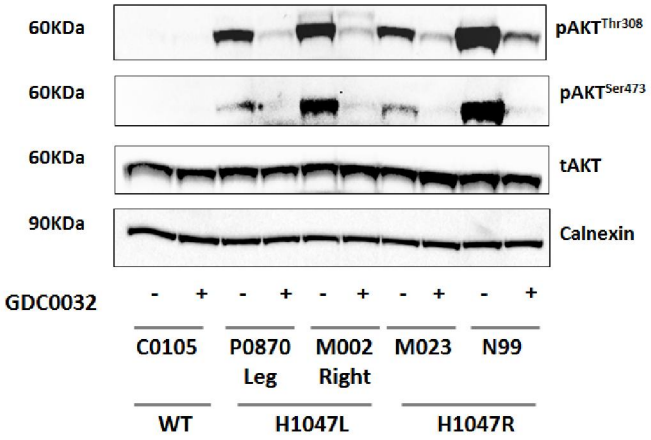


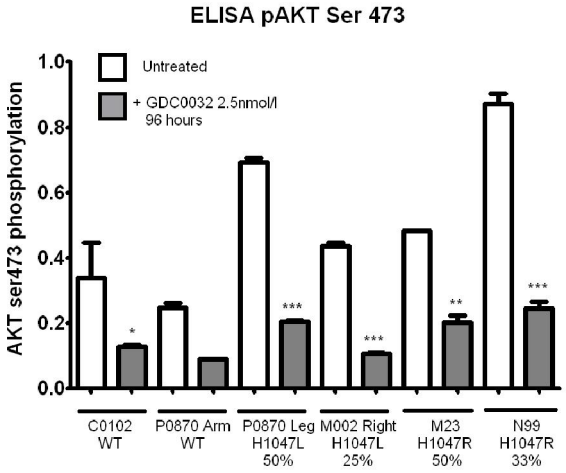


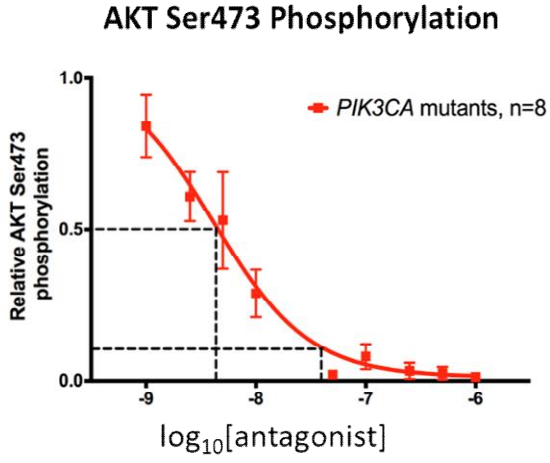
Alpelisib and PROS – My thoughts

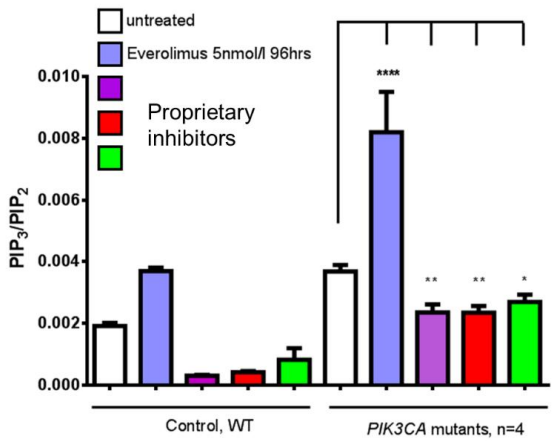
Does alpelisib have a beneficial impact on PROS? - *Probably*
How large is the effect? - *We don't know*
How much does it vary among different people? - *We don't know*
What is the side effect profile in PROS - *We don't know*
Is it safe in the long term? – *We don't know*
Is it better, the same, or worse than other experimental treatments? – *We don't know*
This case series is encouraging, but registered, formal clinical trials are urgently needed!!!

Effect of p110α Inhibition in Primary Cells









Victoria Parker

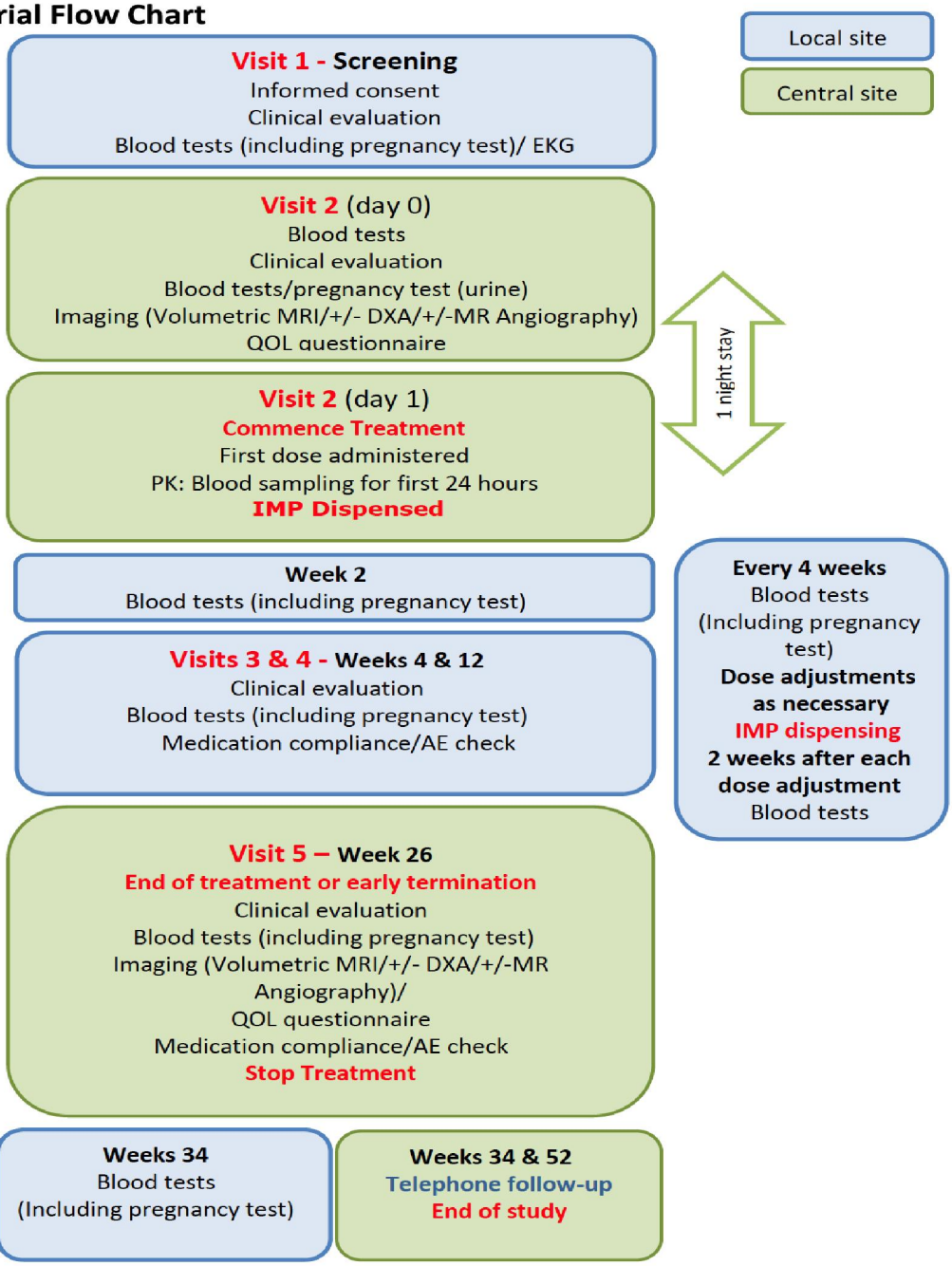
TOTEM Study (Dijon/Manchester)

A Multi-Centre, Open Label, Single Arm, Phase IB/IIA, Trial of Taselisib (GDC0032) in PIK3CA-Related Overgrowth

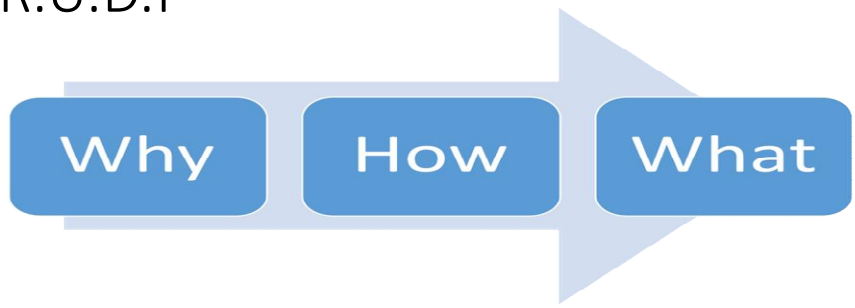
EudraCT Number: 2016-005152-24

18-65y, Male or female, PROS with proven PIK3CA mutation, Stable, No chance of pregnancy, No sirolimus or similar within 12 weeks before assessment, Not <3 months following surgery, No chronic diarrhea, poorly controlled diabetes, lung inflammation, liver or kidney impairment

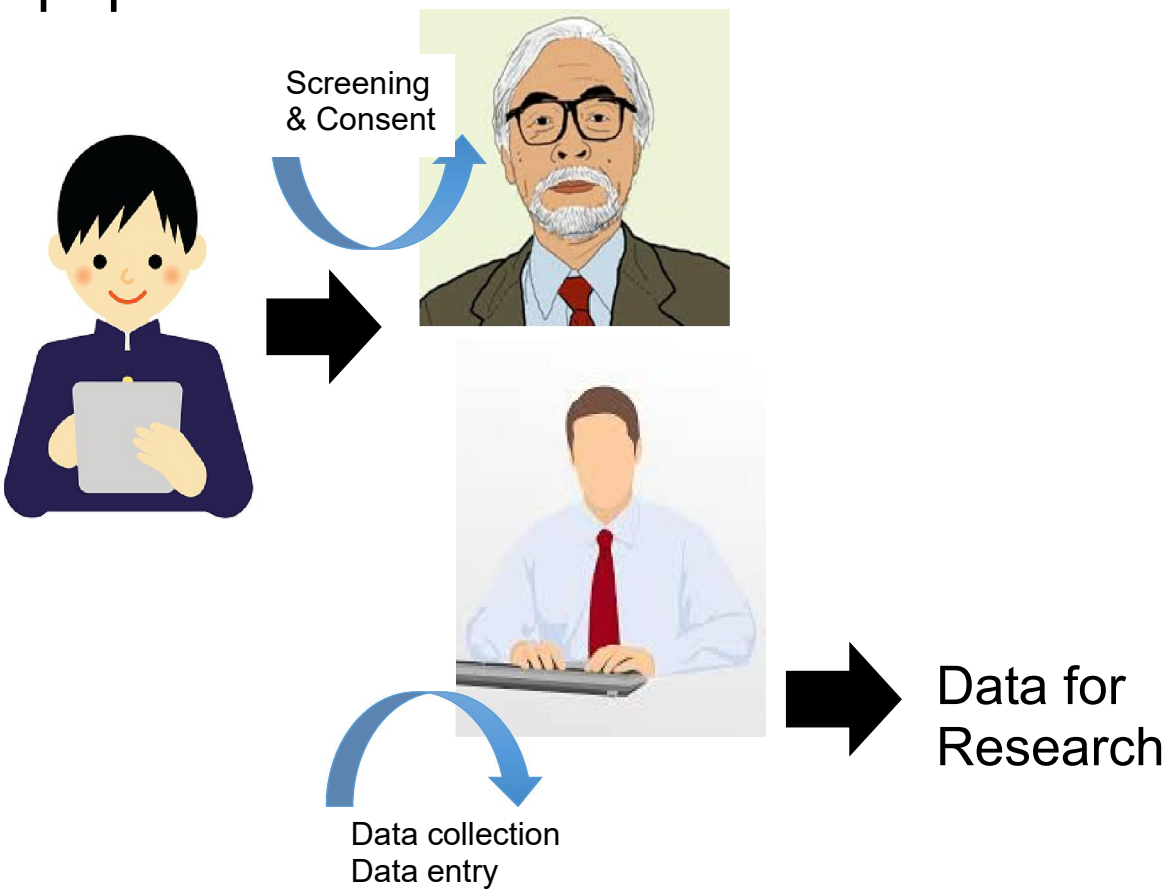
6 Trial Flow Chart



*R*are and *U*ndiagnosed *D*isease Stud*Y*
R.U.D.Y



Traditional pathway: face to face and paper based



Novel pathway: face to face and paper based

Online consent

Authentification process

Data for researchh

Benefits
- Disease record
- Disease progression
- Patient forum
- Research availability

Why is RUDY different from other research studies?

Easy to use
Safe
Personalized
Rewarding

Directly enter data

Partner / family

See how researchers use your data

See/ use what you have entered

Low effort

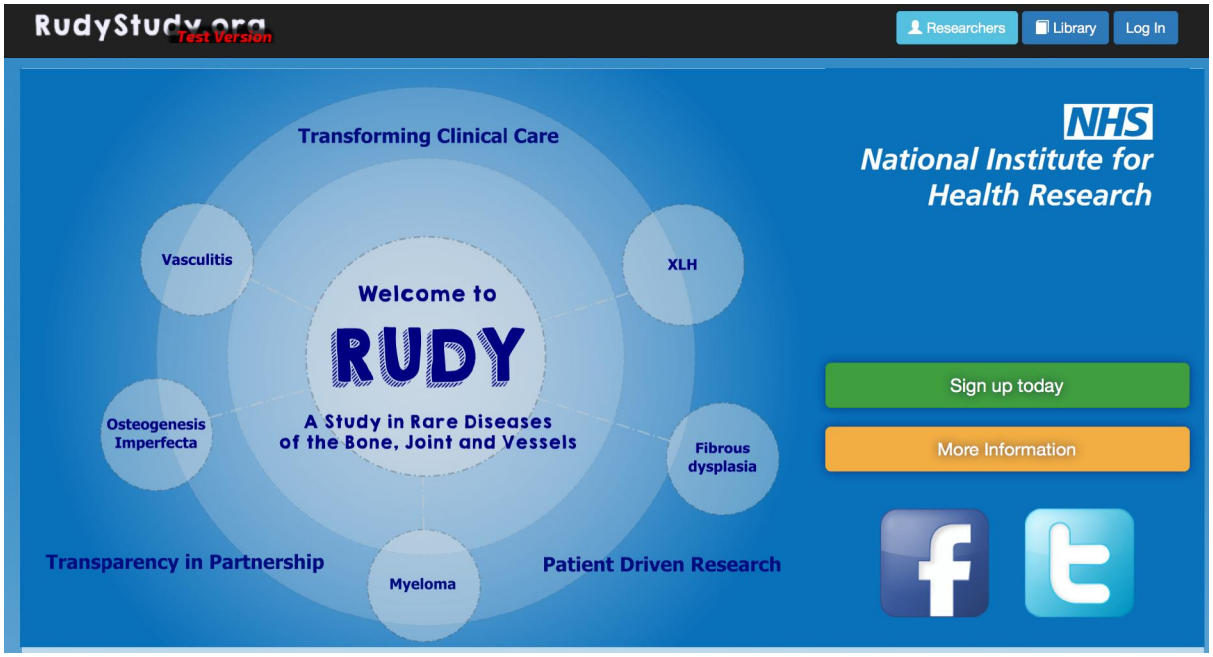
Use data for research

Record your paraprotein levels

Why do we need RUDY for overgrowth syndromes?

1. Recruit patients for testing new medications across the NHS with different types/ progression of their overgrowth syndrome

2. How current patients are being treated by the NHS in terms of
    1. How they got diagnosed
    2. Ongoing NHS care
    3. Quality of life



RUDY

Asked questions relevant to your condition

Easy to use
Safe
Personalized
Rewarding

Works online –
Join any time
Complete questionnaires any time
Get in touch any time

Can see all your data
Own Personal disease record. See how researcher use your data

Can join our active patient forum and direct how RUDY develops

Meets University and UK government standards for data security
Only you and the Rudy Administrators can see your personal information

Participant ***entered*** data

Timeline

Diagnosis History
Fractures
Medications
Radiotherapy
Chemotherapy
Stem Cell Transplants
Transfusions
Spine Cement
Bone Specific therapy
Anaesthetic

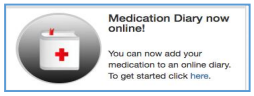
MYELOMA: treatment at diagnosis

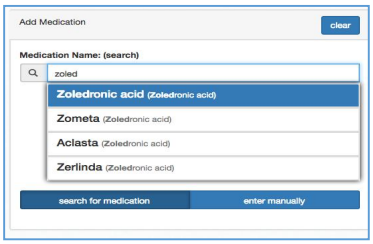
FIBROUS DYPLASIA: classification and staging

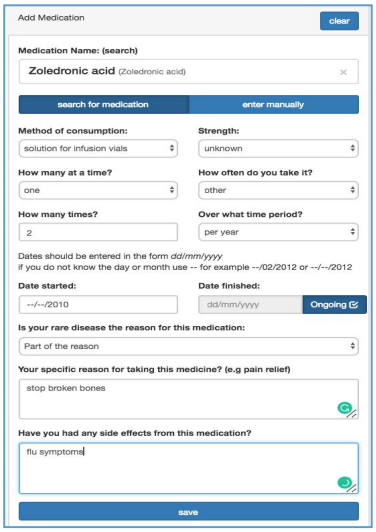
6 monthly online questionnaires

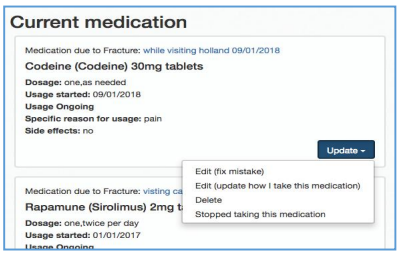
ALL DIAGNOSES: EQ5D-5L, SF-36,
Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale,
McGill pain, Brief pain inventory short form, PainDetect,
Hospital Anxiety and Depression scale, Functional Assessment of Chronic Illness Therapy- Fatigue (FACIT-F), Nottingham ADL score, Barthel Index, MRC fatigue Scale, Walk 12, Anaethetic Questionnaire
CANCER: QLQ-C30,
MYELOMA: MY20
VASCULITIS: Vasculitis PROM

CHILDREN
PedsQL4.0, CHAQ, QoL Paediatric and the Wong-Baker Faces questionnaires

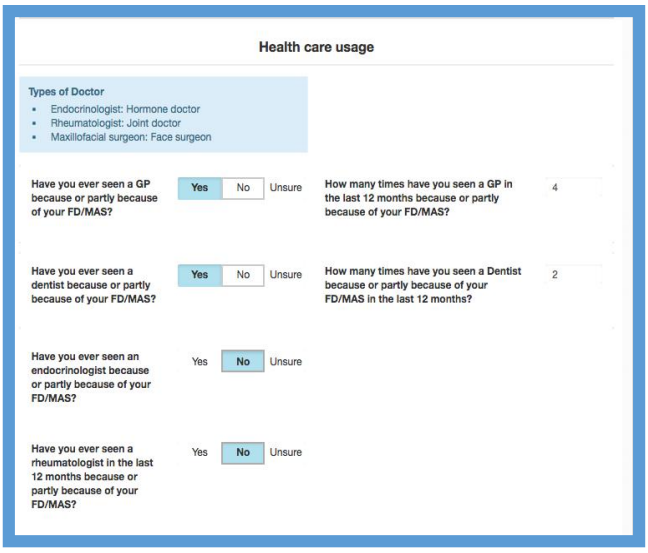

Medication Diary now online!
You can now add your medication to an online diary. To get started click here.

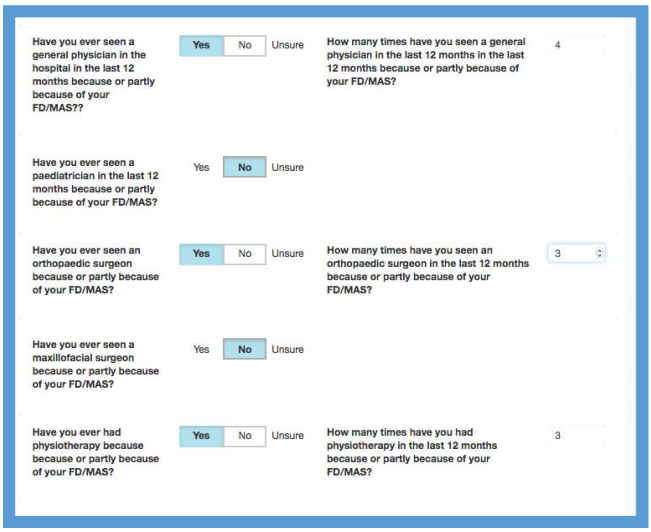

Add Medication
clear
Medication Name: (search)
zoled
Zoledronic acid (Zoledronic acid)
Zometa (Zoledronic acid)
Aclasta (Zoledronic acid)
Zerlinda (Zoledronic acid)
search for medication
enter manually


Add Medication
clear
Medication Name: (search)
Zoledronic acid (Zoledronic acid)
search for medication
enter manually
Method of consumption:
solution for infusion vials
Strength:
unknown
How many at a time?
one
How often do you take it?
other
How many times?
2
Over what time period?
per year
Dates should be entered in the form dd/mm/yyyy
if you do not know the day or month use -- for example --/02/2012 or --/--/2012
Date started:
--/--/2010
Date finished:
dd/mm/yyyy
Ongoing
Is your rare disease the reason for this medication:
Part of the reason
Your specific reason for taking this medicine? (e.g pain relief)
stop broken bones
Have you had any side effects from this medication?
flu symptoms
save

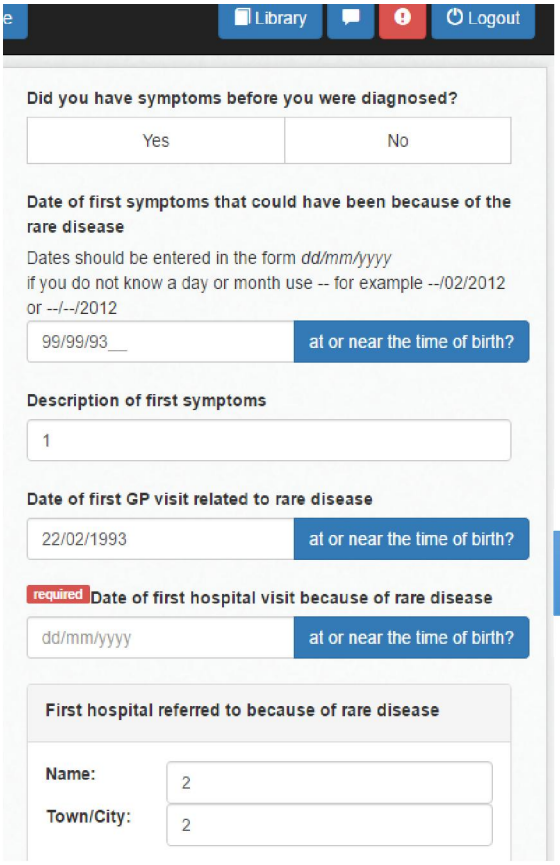

Current medication
Medication due to Fracture: while visiting holland 09/01/2018
Codeine (Codeine) 30mg tablets
Dosage: one,as needed
Usage started: 09/01/2018
Usage Ongoing
Specific reason for usage: pain
Side effects: no
Update
Edit (fix mistake)
Edit (update how I take this medication)
Delete
Stopped taking this medication
Medication due to Fracture: visting ca
Rapamune (Sirolimus) 2mg t
Dosage: one,twice per day
Usage started: 01/01/2017

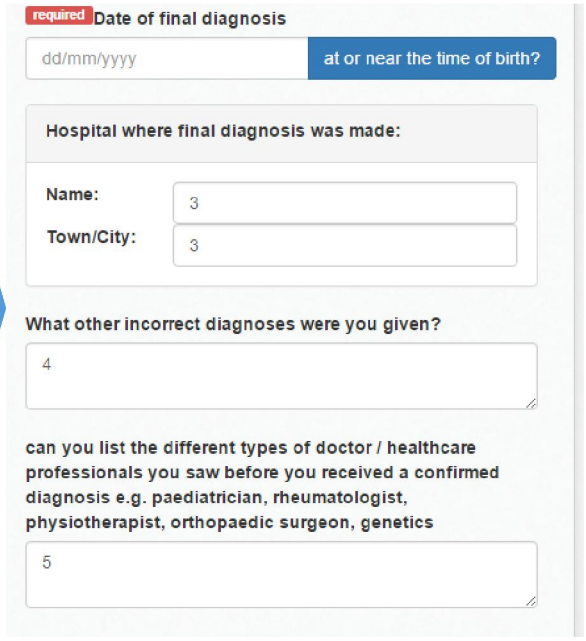

Previous medication
Testosterone (Testosterone)
as needed
Usage started: 01/10/2015
Usage finished: --/03/2016
Rare disease: The main reason
Side effects: 5
Update
Medication du
Prednisolo
Dosage: a half
Usage started
Usage finishe

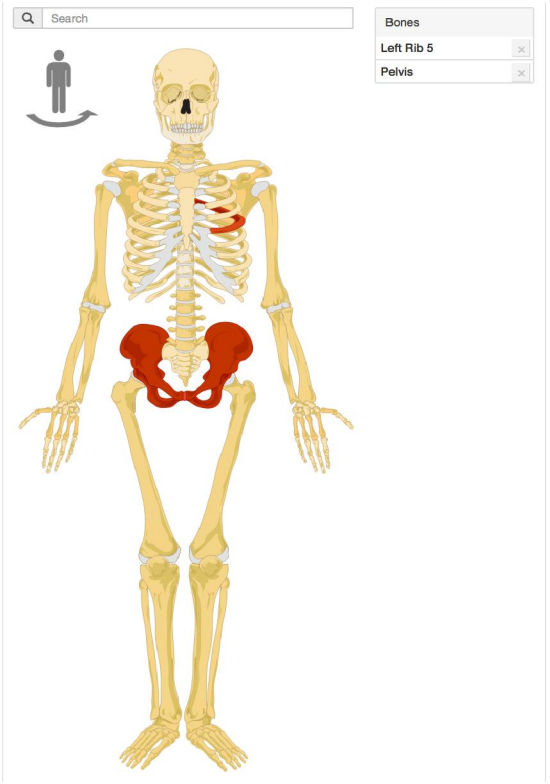

Health care usage
Types of Doctor
Endocrinologist: Hormone doctor
Rheumatologist: Joint doctor
Maxillofacial surgeon: Face surgeon
Have you ever seen a GP because or partly because of your FD/MAS?
Yes
No
Unsure
How many times have you seen a GP in the last 12 months because or partly because of your FD/MAS?
4
Have you ever seen a dentist because or partly because of your FD/MAS?
Yes
No
Unsure
How many times have you seen a Dentist because or partly because of your FD/MAS in the last 12 months?
2
Have you ever seen an endocrinologist because or partly because of your FD/MAS?
Yes
No
Unsure
Have you ever seen a rheumatologist in the last 12 months because or partly because of your FD/MAS?
Yes
No
Unsure

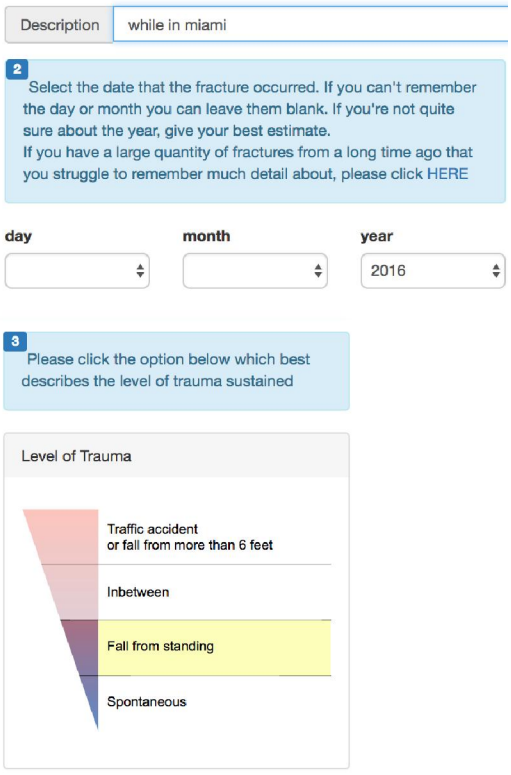

Have you ever seen a general physician in the hospital in the last 12 months because or partly because of your FD/MAS??
Yes
No
Unsure
How many times have you seen a general physician in the last 12 months in the last 12 months because or partly because of your FD/MAS?
4
Have you ever seen a paediatrician in the last 12 months because or partly because of your FD/MAS?
Yes
No
Unsure
Have you ever seen an orthopaedic surgeon because or partly because of your FD/MAS?
Yes
No
Unsure
How many times have you seen an orthopaedic surgeon in the last 12 months because or partly because of your FD/MAS?
3
Have you ever seen a maxillofacial surgeon because or partly because of your FD/MAS?
Yes
No
Unsure
Have you ever had physiotherapy because because or partly because of your FD/MAS?
Yes
No
Unsure
How many times have you had physiotherapy in the last 12 months because or partly because of your FD/MAS?
3

Diagnostic Delay





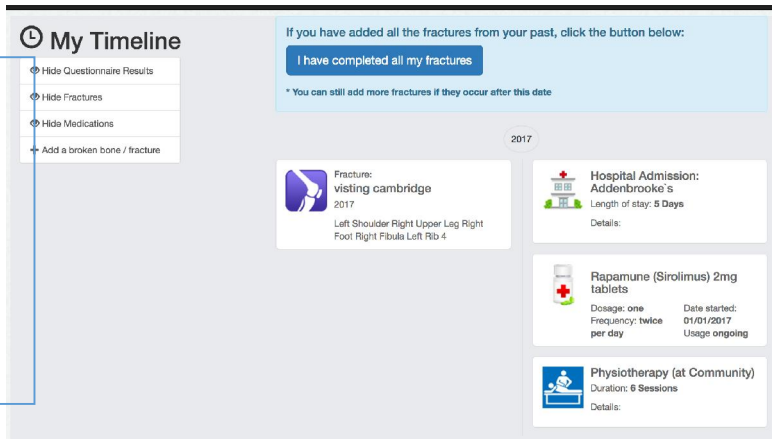




Why

Participant benefits

Can see all your data
Own Personal disease record
See how researcher use your data



Professor Jane Kaye
Professor of Health, Law and Policy & Director, HeLEX

Nuffield Department of Population Health
University of Oxford

Have to have informed consent to take part in most research studies

Have the information

Understand the information

Freely agree to take part

Is that decision Fixed over time?

What's in it for me?

Finally for 2018

It has been an amazing year for GoPI3Ks both in terms of fundraising but also in being able to help others. It was wonderful to be able to host our first family weekend. I certainly underestimated how much of an effect this would have for patients & families alike & especially for those who had never met anyone else with PROS.

A big thank you goes to those who helped make this weekend possible, those kind people who donated funds, the doctors for sharing their expertise & the patients & families for attending.

Lastly your GoPI3Ks team, Me (Mandy Sellars), Yvonne Tierney-Neave and Sue Harper want to wish you a very MERRY CHRISTMAS & wonderful New Year. xx