# NEWSLETTER

**Genetic Overgrowth PI3K Support**
**www.gopi3ks.com**

**December 2017**

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.

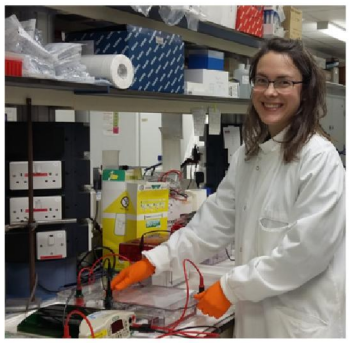
Recent developments from the research team at Addenbrookes, Cambridge:

Prof Robert Semple
Lead of the Segmental Overgrowth Study

It's been a busy year in the lab, and also a year of change, not least as I am moving to take up a new research position at the University of Edinburgh, although I shall be keeping close links with the Cambridge team, including the new NHS clinic run by Dr Bowdin. We have made much progress in finding specific diagnoses for people with overgrowth problems, and the new information we have gained is allowing us to give increasingly accurate outlooks for those we diagnose. Most satisfying to me is the transition of some of the research tests we have developed into NHS clinics where they are accessible for the whole country without being part of a research study. I'm also convinced that our link up with the RUDY study described at the end of the newsletter offers a great opportunity to improve clinical care and find new treatments, especially when combined with some of the exciting basic research studies underway in the lab, such as those involving stem cells. RUDY also provides a really useful way to store lots of complicated information that can be shown to doctors when needed. So, these are exciting times, although there is much work ahead.

## WHAT HAVE WE LEARNT ABOUT SEGMENTAL OVERGROWTH SO FAR?

After three years of recruiting patients and investigating gene changes causing patchy, asymmetric forms of overgrowth, we have made major progress in identifying the genetic cause in many patients. Over 70 study participants have now visited us at the Clinical Research Facility in Cambridge, and we have provided genetic testing for a further 250 people referred from all over the world. Thanks to all of them, we are in the process of writing a scientific paper to summarise our experience, which we hope will contribute to improving diagnosis testing and clinical management for overgrowth patients in the future.

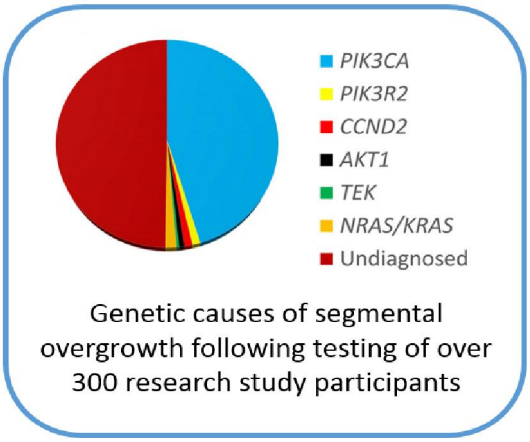


Rachel Knox,
Research Assistant

So what have we learnt?

- To give the best chance of getting a genetic diagnosis, a small skin biopsy must be taken from an affected area of the body. We have also had success diagnosing several children with M-CM and MCAP by taking a saliva swab. Sometimes the genetic change may be found by taking a blood sample, but chances are much increased by testing affected skin tissue instead.
- We have on several occasions tried to perform genetic testing using stored tissue from previous surgeries. However this has very limited success – the method of preserving tissue badly damages DNA, and this poor quality DNA makes the genetic testing results difficult to interpret.

- 45% of study participants have genetic changes in the gene called *PIK3CA*. The most common changes are p.H1047R, p.H1047L, p.E542K, p.E545K and p.E726K – these numbers describe the part of the protein which is altered, causing a hyper-activated form of this growth switch to be made.
- Another 5% of participants have changes in other genes which also control growth, including those named *KRAS*, *PIK3R2*, *TEK*, *AKT1* and *CCND2.*

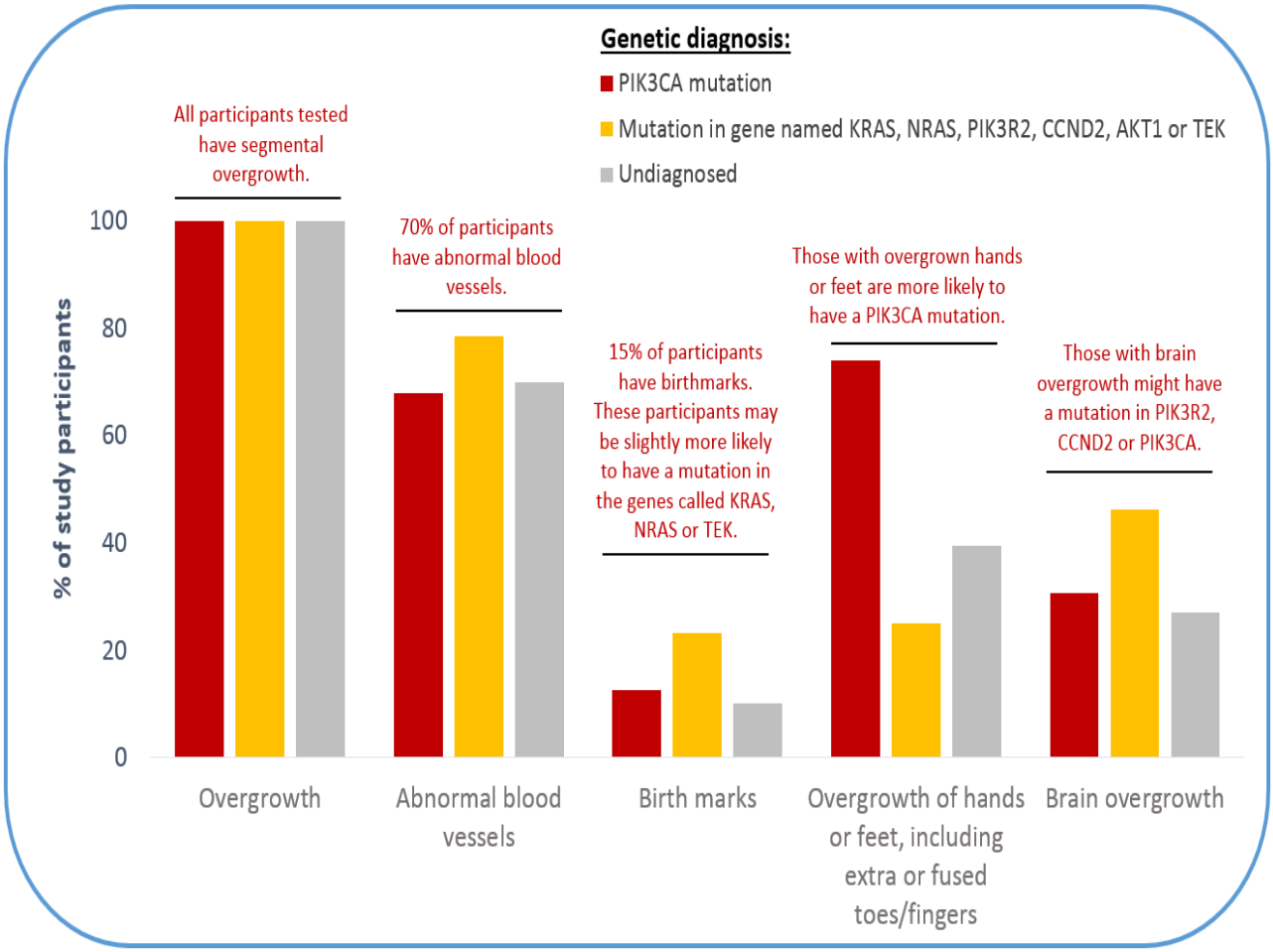



Genetic causes of segmental overgrowth following testing of over 300 research study participants

- The remaining 50% of study participants remain undiagnosed. Due to the mosaic, patchy nature of the condition, repeating the testing by having a second biopsy may be worthwhile in some cases. When repeat testing remains negative, we are still trying to identify additional genes which could be causing the condition.

## IS THERE A LINK BETWEEN GENETIC DIAGNOSIS AND CLINICAL FEATURES?

A question we have been thinking about a lot is, can we tell who is likely to have a *PIK3CA* mutation from their clinical presentation? We think that patients with severe overgrowth, which is distinctly localised to only one part of the body, are more likely to have one of the most common changes in *PIK3CA*, for example, p.H1047R. However, for the more diffusely affected patients, it seems at the moment almost impossible to distinguish those who will test positive for a *PIK3CA* mutation from those who will not.




## GENETIC TESTING – NOW AN NHS SERVICE

We have now turned our diagnostic testing knowledge into genetic tests available on the NHS via the UK Genetic Testing Network in Cambridge and Manchester. While we are now seeing far fewer study participants on our research facility, we are instead focussing on ensuring that patients and their specialists know how to access these services.

## SPECIALISED OVERGROWTH CLINICS STARTING IN THE ADDENBROOKE'S CLINICAL GENETICS DEPARTMENT

We are delighted to announce that Dr Sarah Bowdin in the Clinical Genetics department here at Addenbrooke's Hospital in Cambridge, has recently started seeing overgrowth patients as part of a dedicated NHS clinic. It is fantastic to be able to transition our expertise into a NHS service, and we very much look forward to working with Dr Bowdin.

Dr Sarah Bowdin
Consultant Clinical Geneticist

## PROMISE CLINICAL TRIAL UPDATE

Dr Victoria Parker
Consultant Endocrinologist

The PROMISE trial has officially now finished and we are currently looking at all of the results from the patients who participated in Cambridge, and also those who participated in the USA and France. We are very close to finishing this process and are hoping to be able to publish the final results early next year. We would like to take the opportunity to thank all of the patients and their parents who participated, for their dedication and commitment to the study.

**PROMISE Clinical Trial:**
***PIK3CA*-Related Overgrowth Multinational Investigation of Sirolimus Efficacy**

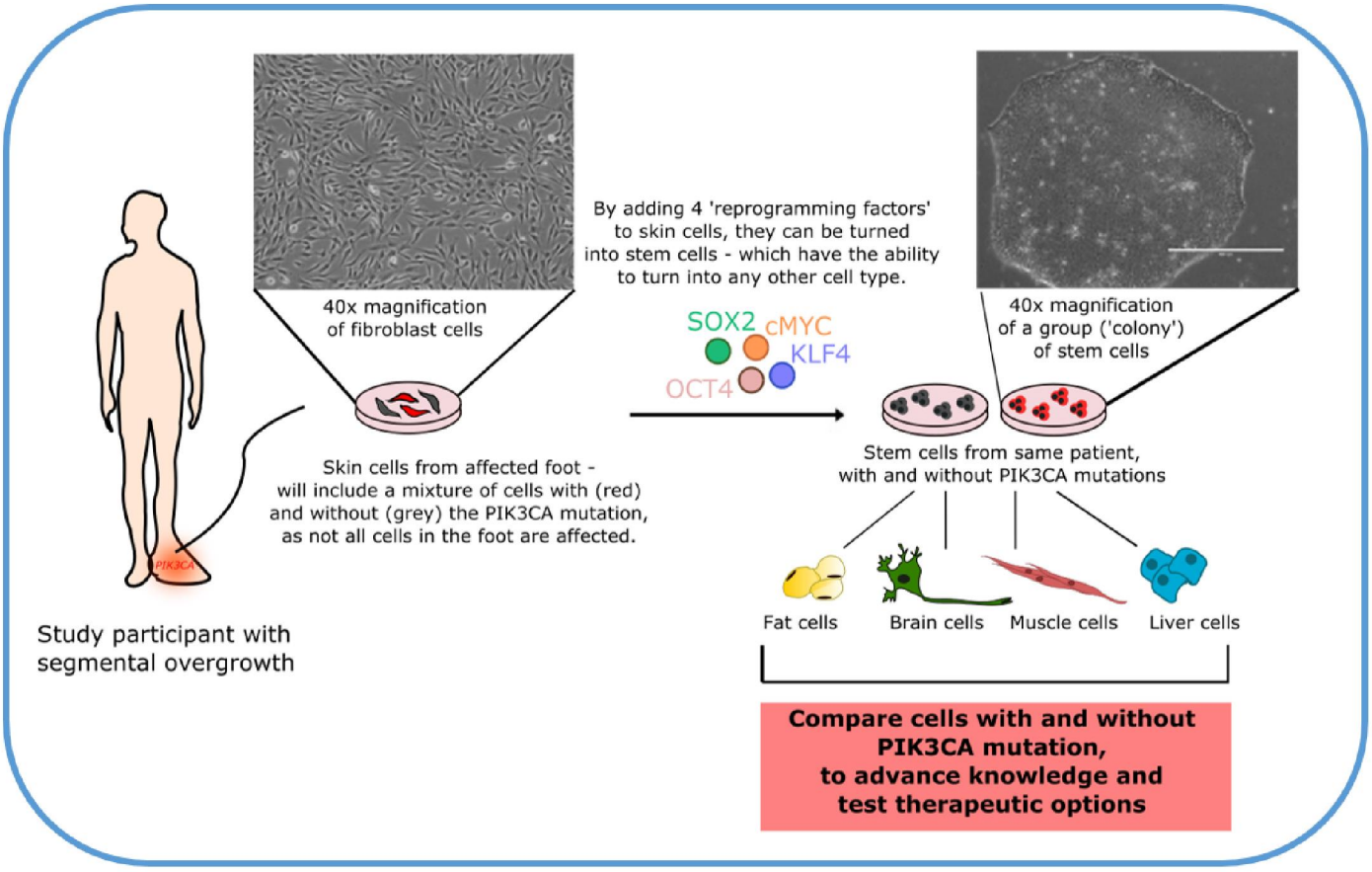
Aim: to discover whether or not sirolimus is an effective medicine to slow down growth in patients with segmental overgrowth. Participants took sirolimus as a pill or syrup for 6 months. We measured their growth and body composition by DXA scan (picture on the right) before and after treatment, as well as monitoring their health regularly.

## ON-GOING RESEARCH – STUDYING OVERGROWTH IN STEM CELLS

Until last year, we were using skin cells grown from patient biopsies to study overgrowth in the lab. We are trying to understand why these genetic changes cause cells to grow faster than usual, and we tested a variety of drugs which might reverse this process. The disadvantage of studying skin cells (called fibroblasts) is that they age quickly when out of the body. They also limit us to looking at only one cell type (skin), when in reality fat, bone and other tissues are also affected.

Ralitsa Madsen,
4th year PhD student

To get around these problems, Ralitsa, a PhD student in our lab, has made stem cells with *PIK3CA* mutations. Stem cells are 'pluripotent' – they can become any cell type in the body. We are able (with permission from study participants) to make stem cells out of patient skin cells, just by adding four chemicals. Looking at stem cells allows us to model the effect of overgrowth mutations (genetic changes) during early human development, which has not been done before.



We have made stem cells with two different *PIK3CA* mutations – p.H1047R and p.E418K. These 'overgrowth' stem cells mirror the characteristics of overgrowth syndromes – the cells survive better under harsh conditions and have a different shape. Ralitsa and the team have already discovered more about the biology of overgrowth, and we hope the cells could be used for preclinical drug testing in the future.

## RUDY – A NEW ONLINE DATABASE ENABLING RECRUITMENT & RESEARCH IN RARE DISEASES

Leena De Silva,
Research Co-ordinator

To advance research into overgrowth further, and in particular A) to gather the information needed to support funding bids for better NHS clinical services, and B) to make sure that people with overgrowth are contactable when trials of new medicines are available to consider, we have partnered with the RUDY Study, led by a team at the University of Oxford and funded by the government through the National Institute for Health Research.

We are very excited about the potential that the RUDY study offers. It provides an excellent platform that will allow participants to self-enrol via a secure online database, allowing access 24hrs a day, 7 days a week to the data you upload so that it can serve as a place to record and organise all the health issues and contacts with professionals that you have seen over the years. We are in the final phase of database design with the team in Oxford for the inclusion of segmental overgrowth, with plans to go live in January 2018.

Participants can build their whole profile, at their own pace; collating pertinent information such as medical history, and prescriptions, creating medical diaries, and accessing various relevant NHS validated quality of life questionnaires, and much

more! This may also provide any reputable research teams (not just us!) with a point of contact for invitations for future trials.

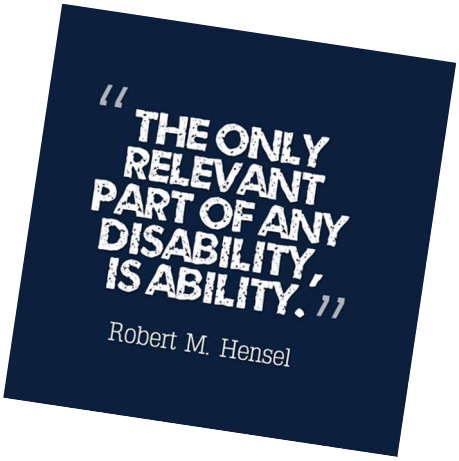
RUDY covers a range of rare disease groups and gives participants the opportunity to be part of a network in the UK as well as being connected to the rest of the world. It not only allows you to build your own profile and history with easy accessibility wherever you are in the world, but also puts you in control of what and how you share your information. RUDY has various levels of consent, enabling you to share as much or as little as you wish to. There is also a participant forum that you are welcome to join and participate in, offering 6 weekly online conference calls to assist in various ways such as developing the platform, feeding back on updates as well as voicing your views on consents and participant information sheets.

We are very enthusiastic about the possibilities of RUDY and encourage you to have a look around the database once live in January 2018. We would also like to ask that you to consider signing up whether a new or current patient of ours. We are confident the database will provide you with a great tool that not only aids research, but may also be of practical value to you. For further information about RUDY, or to sign up, please contact us (email ld489@medschl.cam.ac.uk) or visit Rudy database.

We remain hugely grateful to all our study participants and their families, as without you none of this work would be possible!
For more information, please visit our website, Facebook page or follow us on Twitter:

http://www.overgrowthstudy.medschl.cam.ac.uk/
Twitter #overgrowthstudy
Facebook:https://www.facebook.com/segmental.overgrowthstudy

wellcome trust | NHS National Institute for Health Research | Cambridge University Hospitals NHS Foundation Trust | UNIVERSITY OF CAMBRIDGE

# AMELIA'S STORY

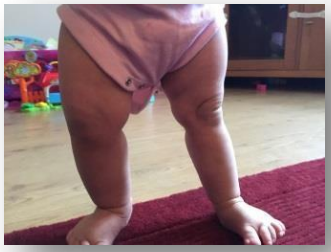
**My Story so far…**

**My name is Amelia; I live in Gloucestershire with my Mummy and Daddy. I was born in July 2015 at Gloucester Royal Hospital. I was born with a few minor medical complaints but generally a healthy baby. Within a few hours of being born it became apparent I had noticeable birth marks across my body and a large purple mark across my forehead. Along with this my right cheek was bruised and swollen which the doctors believed was due to the emergency forceps delivery. I spent 3 days in hospital with my mummy and met many different consultants who were very interested in my birth mark as many of them had not seen this before… I was quite unique **

**Before being discharged from hospital the consultants discovered I had hip dysplasia and would need a harness to strength and support my hip in the early stages of growth (picture of me in my harness which I wore between 6 weeks and 4 months)**

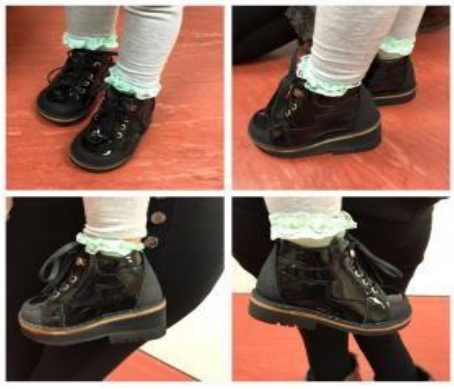
**As the months went on it became noticeable that my facial swelling was not going down and I was referred to a specialist to complete an ultrasound. At this appointment it was also noticed that my right leg and arm was also larger than my left. After many tests and appointments at Gloucester Royal Hospital we were referred to a specialist at Great Ormond Street Hospital who suspected an Overgrowth Condition which was affecting the right side of my body. Between 8-9 months old I experienced two absent seizures and spent a night in hospital where I had an ECG and EIG to find out what was causing them but nothing was found.**

A week after my first birthday I attended GOSH to have a skin biopsy and MRI scan, which tested positive for PIK3CA gene mutation.
As many of you will know this condition varies from person to person and in my case it's causing my right leg to grow at a faster rate than the left making it wider and longer in length. I am being referred to orthotics to get measured for my shoes which will help with the discrepancy in length and size, which will stop me tripping or dragging my leg behind.



The MRI scan picked up the slightly larger size to the right side of my brain, it doesn't seem to affect my development in fact, Mummy and Daddy think this is why I'm too clever for my own good!
My face is noticeably larger on the right and affects my cheek, lip and eye shape but neither of these appear to be affecting my day to day at the moment.

So it's October 2017 and today I collected my orthotic shoes. I was very excited as I chose these at my last appointment. I have had them on all day and seem to be walking better. I go back in 3 months for a check-up and to choose a second pair.

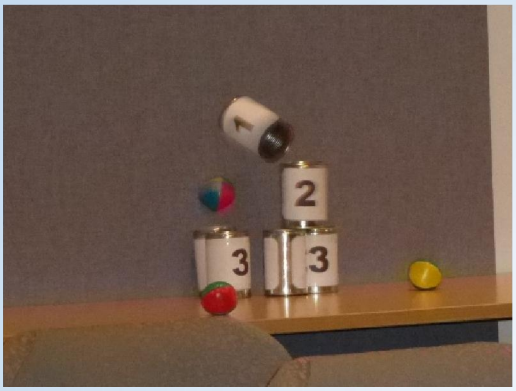


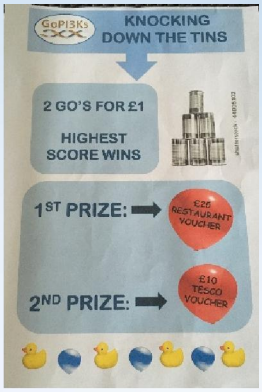
# *FUNDRAISING*

Over this year there has been various 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.

My friend Tara Sturgeon and her work colleagues at Aseptics department, Royal Sussex County hospital fundraised and bought GoPI3Ks pin badges raising **over £100**


Another fundraiser took place in June 2017 called the GoPI3Ks fairground. We had various games such as knocking down the tins, hooking the hoops & throwing darts for the highest score as well as a tombola, prizes of restaurant vouchers, alcohol, chocolates & guess the number of sweets in a HUGE jar.



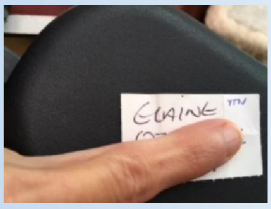

AN AMAZING £420.73 WAS RAISED.

An auction on e-bay to win a helicopter ride experience that was kindly donated by Joanne Brookes was won By Rachel Douglas, raising **£56** for GoPI3Ks. Thank you Rachel

A huge thank you goes to Di McInnes in Burnley for your kind donation of **£121** following Lowerhouse Pride on 14/10/2017

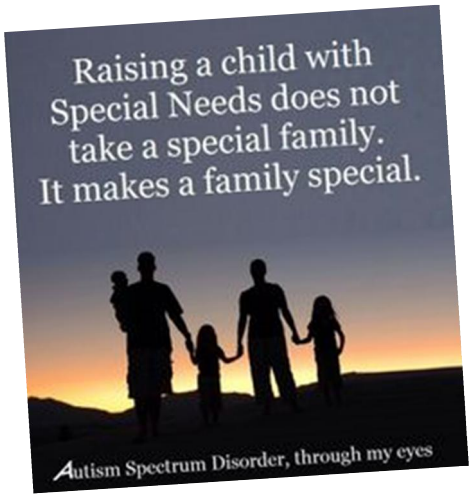

We raffled the chance to win an Indian meal for 2 at the Agra (Hapton, Burnley, Lancashire) The lucky winner was: Elaine, who we hope had a fantastic evening. A BIG thank you goes to the staff at the Agra for their generosity, we raised a total of **£320**. Video of the draw: https://www.fbook.com/mandy.sellars.98/videos/10155930147564319/







Check out their website at: http://www.agrarestaurant.co.uk/AGRA/Welcome.html




In October Kerri, little Amelia (who has the PIK3CA mutation) & her family organised a sponsored walk in aid of GoPI3Ks. They had an amazing turn out as you can see from the photos.

AMELIA'S walk in the rain

GoPI3Ks www.gopi3ks.com

**Come join Amelia**

**on her walk around Stratford Park**

*Help us raise awareness and funds for GoPI3Ks a charity supporting individuals and families who are living with an overgrowth condition.*

| | |
|---|---|
| DATE | Sunday 29th October 2017 |
| TIME | 10:30AM |
| VENUE | Stratford Park Leisure Centre, Stratford Road, Stroud, GL5 4AF |
| DONATIONS | All donations will go to supporting families living with an overgrowth condition |

*Feel free to join us after the walk in the Leisure Centre where you can purchase drinks and food from the café.*

*If you would like to join Amelia please make a donation on the GoPI3Ks funding page https://donorbox.org/gopi3ks also if you are unable to join us but would still like to kindly donate please also visit the funding page, all donations make a difference.*

NUFFY NURSERY A healthy start for your little ones

everyone ACTIVE Stratford Park Leisure Centre

**They raised an AMAZING £1,440**

**NEW FOR 2018 - COMMUNITY CHAMPION**

In October the GoPI3Ks team attended an event at Pendle Powerfest www.pendlepower-fest.com where I spoke about GoPI3Ks & PROS, see the video here: https://www.youtube.com/watch?v=GvkWaaxStWc


From this meeting Pendle Powerfest have kindly made GoPI3Ks their COMMUNITY CHAMPION. This gives us a free pitch at their main event as well as increased exposure throughout the year through their media platforms and smaller events. They also hope to make a small donation depending on how their fundraising goes throughout the year.

From all the team at Addenbrokes &
your GoPI3Ks team, Mandy, Sue & Yvonne
we hope you all have a very


and a wonderful New Year.
I hope that 2018 is filled with lots of love,
laughter and good health.

Thank you for reading our newsletter, if anyone would like to contribute to the next one, or have any ideas for fundraising, please email me (Mandy) at:
gopi3ks@yahoo.com