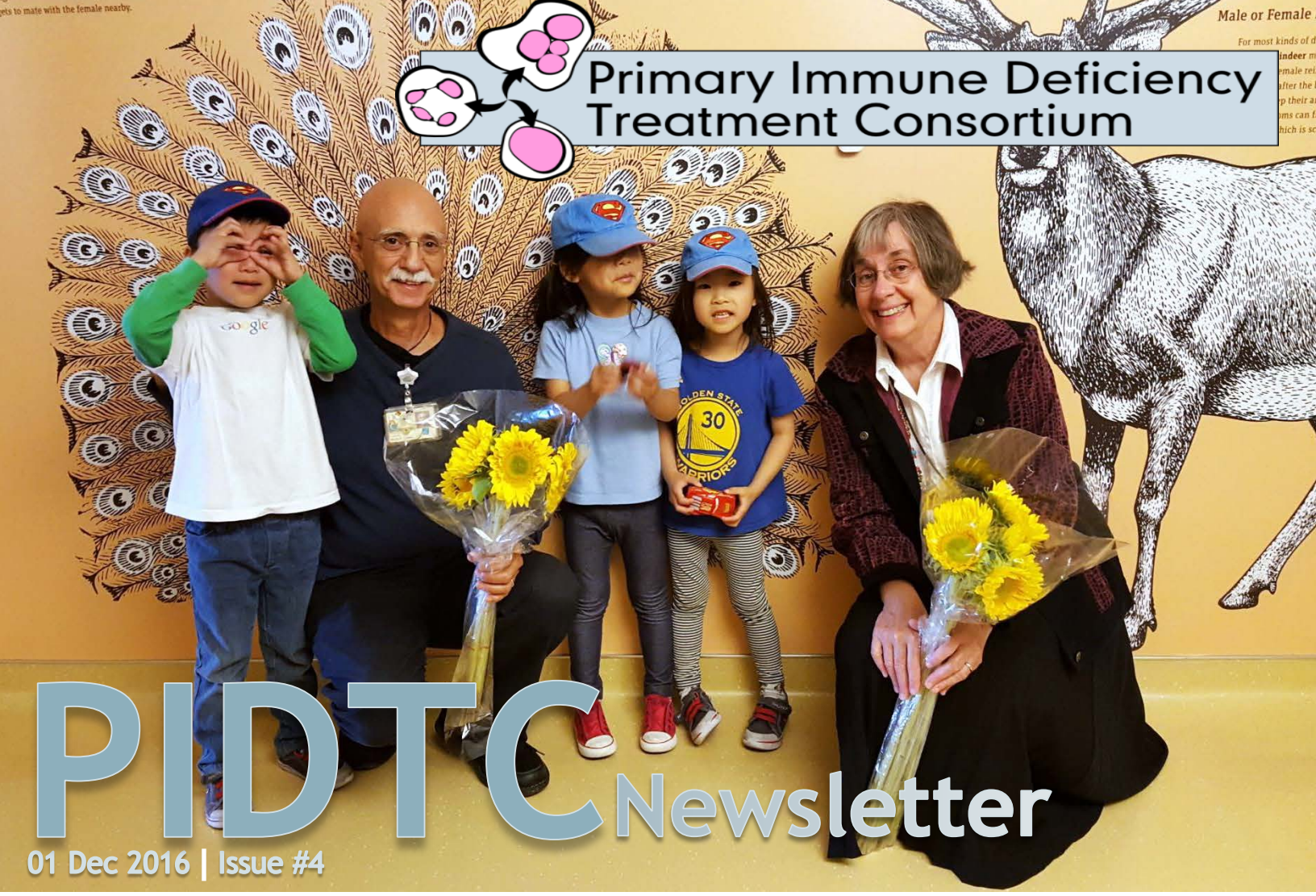


Quarterly Update from Dr. Cowan

As we welcome the next quarter I just want to thank everyone for their continued hard work. We have built up some excellent momentum going into the holidays, especially in the 6903 and 6904 retrospective studies, and I hope to keep this going throughout the next year!

We have had a number of changes implemented this funding year. Firstly, I would like to extend my greatest appreciation to **Dr. Luigi Notarangelo** for his incredible work as the co-PI of the PIDTC. Since Gigi has moved to the NIH from Boston Children's Hospital he will no longer be able to serve as co-PI on the PIDTC studies. He will be stepping down as of January 2017 and **Dr. Don Kohn** at UCLA will become co-PI of the PIDTC. Gigi will continue to work closely on the PIDTC studies and serve on the PIDTC Steering Committee. Thank you both for your dedication!!

Another big change will be the transferring of all PBMTC sites contracting via CHLA to directly contracting with UCSF. This should speed up and simplify the lengthy agreement process. PBMTC centers will now be responsible for submitting their own invoices for their patient reimbursements following the finalization of their contracts. Please check out the announcements in this issue for further details.

I am also very excited to announce that thanks to the incredible work done by the UCSF contracting team and PIDTC project management team we were able to increase the rate of our patient reimbursements for transplanted patients from $800 to $1200! We are working very hard at the PIDTC to help centers better manage the workload of the PIDTC studies!

Finally, it's that time of year again where we begin looking forward to the next PIDTC annual Scientific Workshop and Education Day. This year we will be travelling to Bethesda, MD where the meeting will be hosted by **Linda Griffith** at the NIH. I look forward to seeing you all at Education Day on May 23, 2017 and/or at the Workshop on May 24-26, 2017!

I hope your Thanksgiving was fun and that you and your families have a healthy and happy holiday season and a peaceful New Year,

-Mort

IN THIS ISSUE

PAG Update

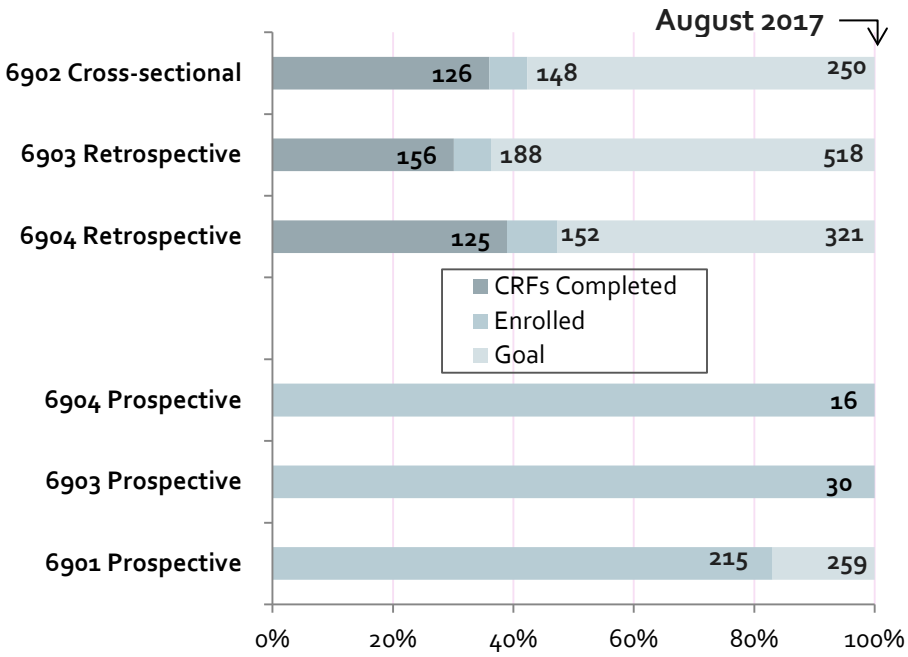
Many of you are aware that we have a contact registry available on our website that allows patients to sign up and ask more about participating on our studies. We have made a lot of progress in connecting PID patients across the country with our studies thanks to the incredible help of our Patient Advocacy Groups: SCID Angels, the IDF, and WAF with special thanks to **Barb Ballard** with the IDF and **Heather Smith** with SCID Angels! The annual IDF conference will be held June 15-17th 2017 in Anaheim, CA this year where Dr. Mort Cowan will have the opportunity to speak about our studies!

We would also like to invite all PIDTC centers to help **Marcia Boyle** and the **IDF** in their effort to provide educational information and support to PID families. The IDF will provide PIDTC centers with IDF Packets that include a number of brochures and materials for families and we will ask that CRAs, social workers, nurses, and physicians at each center make a mindful effort to provide their patients with these much needed resources! More updates to come on the IDF packets from Marcia Boyle.

Immune Deficiency Foundation

Wiskott-Aldrich foundation

CURRENT ENROLLMENTS AND GOALS:



For any inquiries regarding PIDTC patient accrual or DMCC related inquiries please contact the DMCC project manager, Rosalie Holland at Rosalie.Holland@epi.usf.edu

RARE CLINICAL DISEASES RESEARCH NETWORK
Initiative of the National Center for Advancing Translational Sciences (NCATS)

6901 Prospective SCID Update

Our First 100 patient's manuscript is currently being reviewed by the PIs and we are hoping to submit to *Blood* shortly. We would like to thank **Dr. Jennifer Heimall** of CHOP and **Dr. Chris Dvorak** of UCSF and our fabulous statistician, **Dr. Brent Logan** of the Medical College of Wisconsin for all of their hard work on the manuscript and to all the centers, including the physicians and CRA's who contributed patients and completed the CRFs for the first 100!

With the conclusion of the 6902 data clean up nearly complete, we will begin the data clean-up for all 6901 patients beyond just the first 100 enrolled.

The 6901 V4.0 protocol revisions will be released soon! Significant changes to the 6901 protocol include following patients beyond 4 years post-transplant to capture late effects, the inclusion of T cell exhaustion studies, and updates to the eligibility criteria! Stay tuned for the release coming shortly!

Please contact **Tara Bani** at Tara.Bani@ucsf.edu for 6901 inquiries.

PIDTC Patient Highlight

UCSF'S JASON

Jason is a SCID patient cared for at UCSF. Here he is during a recent follow up visit making funny faces with his two superhero sisters and his two favorite doctors, Dr. Cowan and Dr. Puck!

The PIDTC wants to hear about your patients! If you would like one of your patients featured in next quarter's issue, Please send a photo and a brief blurb to Megan.Murnane@ucsf.edu

6902 Retrospective and Cross-sectional SCID Update

We have been undergoing an extensive clean-up of the 6902 retrospective data sets. The near completion of this massive feat is largely thanks to **Brent Logan, Elie Haddad,** and **Tara Bani,** and the rest of the **6902 protocol team.**

URGENT REMINDER: **Sites should be recruiting for the 6902 Cross Sectional Study!**
We cannot emphasize enough the importance of recruiting 6902 patients in for a cross sectional visit and we ask that all centers make a large push this year to do so. Our goal is to bring in an additional 125 patients for a cross-sectional visit through this year and next by August 2017. Sites will receive a reimbursement of $750 per patient enrolled for a cross-sectional visit and CRF completed! To make the process easier we are making it possible for centers to do a cross sectional visit over the phone using a revised consent and interview script. We will also provide centers with instructions on how to enroll patients onto 6902 for the cross-sectional cohort only (if missed enrollment onto 6901 and not already on 6902 retro). Please be sure to attend upcoming conference calls for these instructions and updates. We also would like to remind centers that Megan Murnane may contact you in the near future regarding patients that have signed up on the registry in hopes of participating on a 6902 XS visit! Patients have already consented to the ability for us to share PHI, so any help we can get in coordinating the visit is essential!

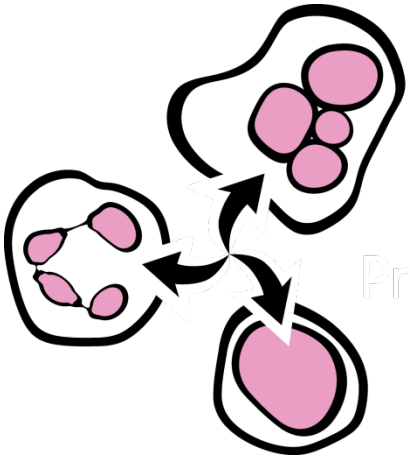
In addition, we would like to remind centers to be sending the optional study samples for the cross sectional visits, especially samples for the **T cell exhaustion study** to the Decaluwe lab.

The 6902 V4.0 protocol revisions will be released soon! Some changes to the 6902 protocol include the phone consent and interview to complete cross-sectional visits over the phone, and the ability to conduct subsequent follow-up visits! Stay tuned for the protocol release coming shortly!

60% of goal

148 ***6902*** *Cross-sectional visits to reach our goal of* ***250*** *total visits by August 2017*

Please contact **Tara Bani** at Tara.Bani@ucsf.edu for 6902 inquiries



6903 Chronic Granulomatous Disease & 6904 Wiskott - Aldrich syndrome Update

We just concluded our 6903/ 6904 retrospective November 30th deadline where the goal was to complete CRFs for 193 CGD retrospective patients and 156 WAS retrospective patients. As of today we have completed **156 CGD** retrospective patients and **121WAS** retrospective patients. Please see the details below on our goals for the remaining two deadlines this year towards completion of the 6903 and 6904 retrospective studies. We cannot emphasize the importance of meeting these deadlines, as we are hoping to do a preliminary analysis shortly and a full analysis of all completed patients by August 2017. **Specifically, we want centers to focus on patients for both 6903 and 6904 that were transplanted since 2010 first so we can analyze and publish papers on these WAS and CGD cohorts.**

Our project manager, Megan Murnane, will be sending out notices shortly to each site regarding the **November 30th Deadline** and what is expected for the next deadline, **February 28th 2017.** A number of centers are behind on these deadlines and we ask that all centers dedicate time to these enrollments and CRFs as soon as possible. Please contact Megan Murnane at Megan.Murnane@ucsf.edu for any questions regarding the expected numbers of CGD and WAS retro patients for your center.

We recognize that centers have been putting forth great effort into completing the workload for these retrospective studies in particular, so we are incredibly excited to announce that we are increasing the reimbursement rate for transplanted patients from $800 to $1200 for all patients enrolled during year 8 (ideally half of the total retrospective patients being enrolled at your center). If you enrolled less or more than half of your retro patients during the past funding year the reimbursements will be adjusted so that exactly half of the patients will be reimbursed at the $800 rate and half will be reimbursed at the $1200 rate.

Centers have all received notice, but we would like to remind center that the PPD/ DAIT is no longer collecting regulatory items for the 6903 and 6904 studies. All items instead should be continued to be uploaded to the eReg binder on the DMCC website and sent to the project management team at UCSF: Elizabeth Dunn (Elizabeth.Dunn@ucsf.edu), Megan Murnane (Megan.Murnane@ucsf.edu) and Tara Bani (Tara.Bani@ucsf.edu).

30% of goal

156 ***6903*** *CGD retrospective patients enrolled and completed of* ***518*** *total patients by* ***August 2017***

38% of goal

121 ***6904*** *WAS retrospective patients enrolled and completed of* ***321*** *total patients* ***by August 2017***

Please contact **Megan Murnane** at Megan.Murnane@ucsf.edu for 6903 and 6904 inquiries.

2016 PIDTC Leadership Meeting Recap

This year the PIDTC Leadership Meeting was held at the NIH in Bethesda, MD on Nov 14th and 15th. The PIDTC Leadership and Protocol PIs gathered to discuss the PIDTC's progress, plans, goals, and aims for each of the current protocols and future protocols. Some of the key topics discussed were:

- Expanding the Steering committee to include 2 new members
- Developed a plan to transition the PIDTC Leadership
- 6901—Upcoming manuscript and future manuscript and study aims
- 6902—Conclusion of the data clean up and analysis for upcoming manuscript
- 6903—Beginning analysis of preliminary retro data and potential manuscripts focusing on patients transplanted since 2010
- 6904— Progress so far for the retrospective study and the start of the initial analysis of the retrospective data
- 6905—Reviewed past study proposal and future study proposal to be submitted to CIRM
- Immune Dysregulation Disorders Study—Discussed study aims and plans for proposal submission in June 2017
- PAG- The IDF introduces IDF packet and brochures to be handed out by PIDTC centers for patients and Parents
- Discussed plans for the grant renewal.

Announcements

New Increase in patient reimbursement rate for transplanted patients!!

In recognition that centers have been putting forth great effort towards the workload for these studies, especially the data entry for the 6903 and 6904 retrospective studies, we are incredibly excited to announce that we are able to increase the reimbursement rate for transplanted patients from **$800 to $1200** for all patients enrolled during year 8 (for the retrospective patients this will ideally be half of the total patients being enrolled at your center). If you enrolled less or more than half of your 6903/ 6904 retrospective patients during the past funding year the reimbursements will be adjusted so that exactly half of the patients will be reimbursed at the $800 rate and half will be reimbursed at the $1200 rate.

We are incredibly appreciative of all the work our investigators and CRAs have been putting into the PIDTC studies and we hope to continue our efforts to alleviate this workload for all centers!

Changes to contracting for PBMTC centers

As of this funding year the PBMTC sites contracting agreements will now be handled directly at UCSF by Kira Bricknell at Kira.Bricknell@ucsf.edu

After the contracts have been finalized, all centers will be responsible for submitting invoices for patient reimbursements. This can be done on a rolling basis as your patient submissions become eligible for reimbursement. These should be sent to the UCSF Controllers office at COAPMail@ucsf.edu

Attention CRAs: 6903 & 6904 Retro Patients: Complete pts transplanted from Jan 1st, 2010 and after FIRST!

We are asking that all centers complete their retrospective patients for the 6903 and 6904 studies that were transplanted from January 1st, 2010 and after before older patients. We ask that they be completed by the Next Deadline. The plan is to begin an analysis and manuscript on these patients shortly.

The PIDTC is expanding: Welcome Alberta!

We welcome the newest PIDTC center, Alberta Children's Hospital, as they join us on all four studies: 6901, 6902, 6903, and 6904. We are excited to have **Dr. Nicola Wright** and her team apart of the PIDTC community!

Be sure to check out our complete list of centers on our website: http://www.rarediseasesnetwork.org/cms/pidtc/

and a map of all our centers on our facebook page: https://www.facebook.com/RDCRN.PIDTC/

Congratulations to our Pilot Project Awardees!

The PIDTC Pilot Project Review Committee is pleased to announce that the PIDTC Pilot Project Award for 2016 will be split between two awardees:

Helene Decaluwe
of CHU Sainte-Justine University Hospital Research Center
"T cell exhaustion in SCID patients with poor T cell reconstitution – Phase 2."

Dr. Decaluwe intends to do a more extended immunophenotypic study of exhaustion markers and to perform RNA-SEQ transcriptional profiling of sorted CD8+ T cells, and sorted T(EM), T(CM) and T(EMRA) cells.

Eric Allenspach
of the Seattle Children's Research Institute
"Characterization of CARD11 defects causing immune dysregulation to better guide therapeutic intervention."

Dr. Allenspach will study novel variants in the PKC-regulatory domain of CARD11 including functional effects and mechanism of action of the new S559 and S652 missense CARD11 mutations found in 2 families with autoimmune disease.

Congratulations to Dr. Decaluwe and Dr. Allenspach!

Mark your calendars for the 2017 PIDTC Annual Workshop!

The 2017 Annual PIDTC Scientific Workshop will take place

May 24-26th, 2017
at the **NIH in Bethesda, MD**

Education Day will held be on May 23rd, 2017

The PIDTC is looking for nominees to expand the Steering Committee!

Our Consortium is soliciting nominations for 2 new North American members of the PIDTC Steering Committee to serve for a 3 year renewable term. **Nominations are due by Friday, December 16, 2016;**

Please request nomination forms and submit by email to Elizabeth Dunn, PIDTC Senior Project Manager, at: Elizabeth.Dunn@ucsf.edu.

We encourage self-nominations and nominations of your colleagues who have contributed to the PIDTC and are willing to participate actively in definition and accomplishment of our scientific, educational and outreach goals. Roles of the Steering Committee members are to prioritize studies and data analysis, oversee all aspects of research and publications, identify outside sources of funds to augment PIDTC activities, and plan and write the competing renewal U54 application for our third five-year term, which must be submitted in October, 2018 or earlier. Future PIDTC research will include continuing focused studies of SCID, CGD and WAS; adding single-gene autoimmune/immunodysregulatory disorders; and participating in collaborative research, including multicenter prospective interventional trials.

The current Steering Committee will select new members, taking account nominee qualifications, primary immunodeficiency expertise, proven ability to obtain competitive research funding, immunology/transplant balance for the Steering Committee membership, diversity concerns and protocol participation by the nominee's PIDTC site.

Attention CRAs: The PPD is no longer collecting regulatory items for 6903/ 6904

As of October 31, 2016 Pharmaceutical Product Development, LLC (PPD) will no longer serve as the Regulatory Management Center (RMC) for PIDTC studies and its functions are being transferred to UCSF. Please contact Megan Murnane (Megan.murnane@ucsf.edu) and Tara Bani (Tara.bani@ucsf.edu) from University of California, San Francisco (UCSF) at the address provided below for further instructions regarding collection of regulatory documents for your site.

Attn: Megan Murnane
550 16th Street, 0434
San Francisco, CA 94143 (FedEx: 94158)

6901 and 6902 V4.0 protocol revisions will be released soon!

Anti C-Kit Clinical Trial for SCID patients who never gained B cells

This Phase I study is a single arm, open label, dose escalation trial being conducted at 2 centers: UCSF Benioff Children's Hospital and Lucile Packard Children's Hospital at Stanford. The study objective is to evaluate the safety and tolerability of tandemly-purified allogeneic $CD34^{+}CD90^{+}$ human stem cells (HSC) in patients with Severe Combined Immune Deficiencies (SCID) conditioned for transplantation with AMG 191, a monoclonal antibody that targets human CD117. It will enroll SCID patients sequentially in three groups based on age: Groups A and B will enroll patients ≥ 12 and from > 2 to ≤ 12 years of age respectively, who have previously undergone an allogeneic human stem cell transplants (HCT) but have low-level donor engraftment and inadequate T and/or B cell function. Group C will enroll patients > 3 months of age with newly diagnosed SCID. Group B will start enrollment after the first dose cohort of Group A has been completed. Group C will start enrollment after the first dose cohort of Group B has been completed. T and B cell reconstitution and function will be assessed by quantitative immunoglobulin, T cell receptor excision circle (TREC) analysis, T cell response to phytohemagglutinin (PHA), and lymphocyte receptor diversity analyses. Patients will be followed for 12 months, and then asked to consent to a second study for long-term follow up.

For questions regarding the trial please contact **Dr. Mort Cowan** (Mort.Cowan@ucsf.edu, 415-476-2659) or **Dr. Chris Dvorak** (Chris.Dvorak@ucsf.edu, 415-476-2188) at UCSF, and **Dr. Rajni Agarwal** (rajnia@stanford.edu, 650-724-7173) at Stanford

EBMT/ IEWP retrospective study on Domino HSCT

"Domino" or serial haematopoietic stem cell transplantation (HSCT) refers to a situation in which the donor of an allogeneic stem cell transplantation has previously received a haematopoietic stem cell transplantation as well. Several case reports have reported successful use of a domino HSCT in patients with severe combined immunodeficiency, suggesting that a domino donor may be a useful alternative to cord blood or adult donors. However, systematic investigation is needed to determine the efficacy domino-HSCT as a treatment modality.

For this reason the Inborn Errors Working Party of EBMT has created a short survey to identify domino transplants. Because of the rarity of this procedure, the PIDTC has been asked to also participate in the data collection. We invite you to complete the survey via the following link: https://www.surveymonkey.com/r/dominotransplant

When your centre has ever performed a domino transplant, we ask you to please complete the study form "*Domino hematopoietic stem cell transplant_20161031*" to document the case. Only when a re-HSCT was performed for the case, the form "*Section3"* will need to be completed as well.

Anyone who contributes a case will be a co-author on the resulting manuscript.

Please return the completed form(s) to the following at your earliest convenience:

Marc Bierings and Mirjam Belderbos, M.E.Belderbos@umcutrecht.nl

HSCT in LRBA deficiency - a joint survey of the IEWP, PIDTC, and ESID

The IEWP is working to compile the existing experience with HSCT in LRBA deficiency. To date, 10 patients have been compiled in Europe and the Middle East (summarized in the attached ESID abstract), and the PIDTC community has been asked to participate to see if any additional patients can be identified in North America.

If you have any patients to contribute to this effort, please send an email to: markus.seidel@medunigraz.at

He will then send you an excel table to complete. Contributors of transplanted patients will of course have a co-authorship on the planned paper.

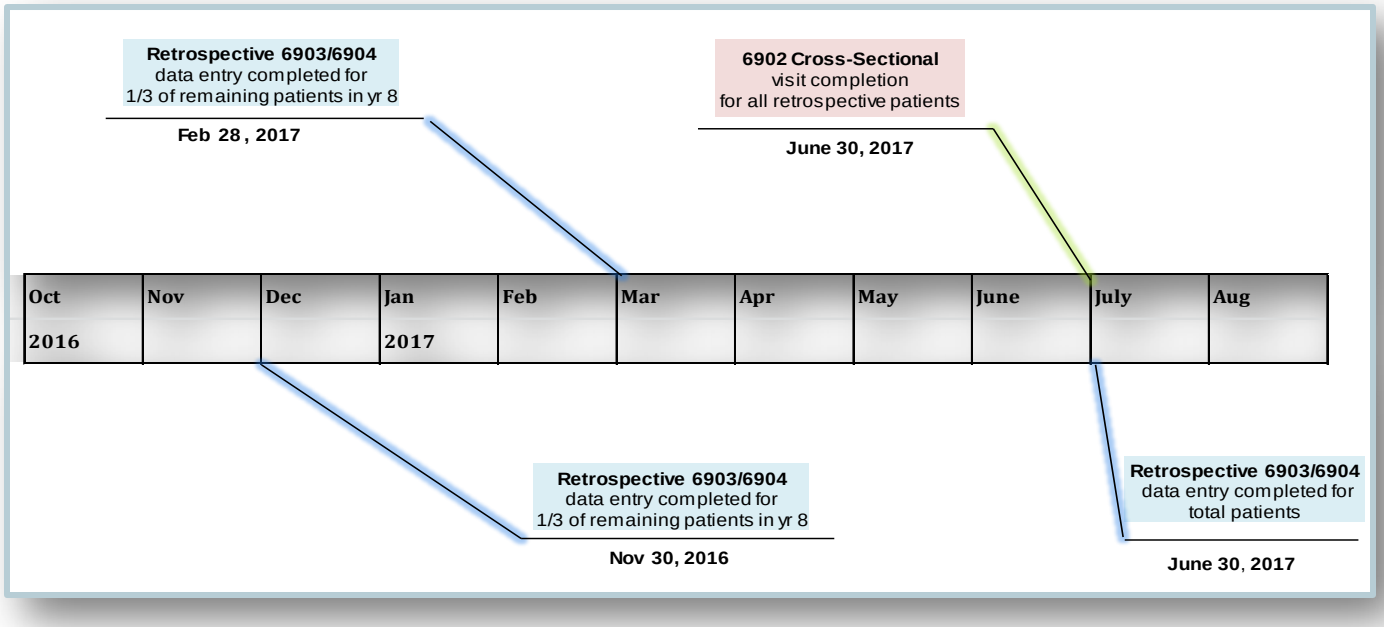
If you are a PID patient and would like to participate on a PIDTC Study…

Join the RDCRN PIDTC Contact Registry!
The Contact Registry is a way for patients with primary immune deficiency and their family members to learn about PIDTC research studies and find out if they may be eligible to participate on one of our studies. Registration is completely voluntary and you may choose to withdraw at any time. There is no cost to join the Contact Registry.
Follow the link to join today:

https://www.rarediseasesnetwork.org/cms/pidtc/Get-Involved/ContactRegistry

Deadlines

Next 6903/6904 Retro Deadline: Feb 28, 2017



We would like to extend our thanks and sincere appreciation for your outstanding support and dedication to the PIDTC. We wish you and your family a wonderful holiday season and a Happy New Year!

On behalf of Elizabeth, Tara, Megan and the PIDTC Leadership Team

PIDTC Newsletter

Brought to you by Megan Murnane and the PIDTC Management Team

RARE Clinical Diseases Research Network

Initiative of the National Center for Advancing Translational Sciences (NCATS)

For questions about PIDTC Newsletter, please contact:

Megan Murnane

PIDTC Project Manager

Megan.Murnane@ucsf.edu

415-476-3837