Learning Health Systems as Facilitators of Precision Medicine

Laura B. Ramsey1, Tomoyuki Mizuno2, Alexander A. Vinks1,2, and Peter Margolis3

1Division of Research in Patient Services, Pharmacy Research, Cincinnati Children’s Hospital Medical Center
2Division of Clinical Pharmacology, Cincinnati Children’s Hospital Medical Center
3James M. Anderson Center for Health Systems Excellence, Cincinnati Children’s Hospital Medical Center

Introduction

The concept of the learning health system offers promise to facilitate personalized medicine. In children, serious illness is uncommon so generating and applying new knowledge therefore requires networks of institutions. To illustrate the concept of the Learning Health System, we describe the example of the ImproveCareNow Network. We then use a network case study to illustrate how the concept of precision medicine can be achieved through a Learning Health System in a real-world clinical environment.

Precision Medicine

The concept of precision medicine is that individual variability is taken into account when deciding a patient’s treatment strategy.(1) The goal of precision medicine is to find the right medication and the right dose for each patient every time. In his State of the Union address in 2015, President Barack Obama launched the Precision Medicine Initiative, introducing the concept of precision medicine to the lay public. Precision medicine includes prevention of disease as well as treatment. Since therapeutics have been developed for the “average patient” historically, there is variability in response. In this speech President Obama said, “What if figuring out the right dose of medication was as simple as taking our temperature?” Precision dosing aims to find the right dose for the patient. What would a system look like that would make achieving this goal as simple as President Obama suggested?

Clinical trials have historically been designed to test the efficacy of a certain dose of medication in a group of patients. Sometimes this dose is based on body size or age, but sometimes not. The clinical research community has struggled with how to do precision dosing in the context of clinical trials, where it takes years to accrue a group of patients. When precision dosing has been attempted in the past through therapeutic drug monitoring (TDM), clinicians thought it was too complicated, and there was no easy interface for the drug monitoring to be included in the patient chart. Now, in the era of the electronic medical record (EMR) and the growing potential to integrate dosing information with the EMR, we are poised to integrate the two tools in order to make TDM feasible in clinical practice. Examples of this approach are beginning to emerge, like clinical decision support...
dashboards that integrate data from multiple sources to provide an individualized dosing regimen.\(^{(2)}\)

Clinical pharmacologists are able to use TDM data to adjust dosages on any given patient in order to achieve a drug level in a therapeutic range; however, this doesn’t happen often for most drugs. The standard FDA-approved dose is based on the average patient, which is designed to produce drug concentrations that are effective in the average patient. In practice, the “average patient” with the average age, average size, and average response does not exist. Since most hospitals and doctor’s offices have moved to using an EMR, the data that could help make medicine more precise is there, waiting to be extracted and analyzed. Treatment outcomes could be improved by harnessing the data in the EMR, especially in large institutions and collaborative groups. What would such a model look like?

**Learning Health Systems**

The Institute of Medicine has promoted the concept of the learning health system in which clinical care and research are integrated.\(^{(3)}\) Learning health systems are a way to harness the power of the electronic medical record, engage patients and clinicians to ask meaningful questions, and make sure that the knowledge that is produced is quickly integrated into care to improve health.\(^{(4)}\) The learning health system is an environment in which the results and outcomes of clinical decisions informs best practices, implementation science, and new research directions.\(^{(5, 6)}\) Furthermore, the role of patients is central to prioritizing research questions and in supporting the research itself.

The Institute of Medicine identified the key features of a learning health system: a participatory, team-based, transparent, improving culture; patient-anchored and tested design and processes; fully and actively engaged patients and public; informed facilitated, shared and coordinated decisions; care that starts with best practices every time; outcomes and costs that are transparent and constantly assessed; ongoing production of knowledge of services and research; a reliable, secure, and reusable resource of health information; trustworthy data that are used for the common good; digital technology that provides the engine for continuous improvement; trust that is actively nurtured and protected; and leadership that is multi-focal, networked and dynamic.\(^{(3)}\) Taken together, these features create a cycle where all healthcare stakeholders deliver high quality care according to best practices and learn how to improve future care. Incorporation of these ideal elements into the learning health system will result in a system that feeds back information and action seamlessly.

The concept of the learning health system offers promise to facilitate personalized medicine. This concept is particularly important in pediatrics. In children, serious illness is uncommon so even the largest institutions may not have enough patients to conduct meaningful research. Generating and applying new knowledge therefore requires networks of institutions. To illustrate the concept of the Learning Health System, we describe the example of the ImproveCareNow Network. We then use the network to illustrate how the concept of precision medicine can be achieved through a Learning Health System in a real-world clinical environment.
ImproveCareNow

Chronic diseases and conditions are the most common and costly of all health problems.\(^7\) Approximately 117 million Americans live with at least one chronic illness and as many as 1.5 million suffer from inflammatory bowel disease (IBD).\(^7{-}^{10}\) IBD is estimated to account for more than 1,300,000 physician visits and 92,000 hospitalizations each year.\(^11\) IBD is also associated with substantial economic burden. The CDC estimates that direct treatment costs for patients with IBD are greater than $6.3 billion per year and indirect costs, such as missed work opportunities, are an additional $5.5 billion each year.\(^11\) Wide variation in diagnostic interventions for and treatment of both adult and pediatric patients with IBD have been reported.\(^12{-}^{18}\)

The ImproveCareNow (ICN) network\(^19,\)\(^20\) began in 2007 with the goal to transform the health, care and costs for all children and adolescents with IBD. With funding from a 2009 NIH transformative research grant, ICN has evolved into an enduring learning health system\(^21\) that harnesses the inherent motivation and collective intelligence of patients, families, clinicians and researchers. All participants work together to accelerate innovation, discovery and the application of new knowledge. Currently, 92 care centers in 36 states, England and Qatar are participating in ICN, encompassing 780 pediatric gastroenterologists caring for 25,400 children, more than 40% all pediatric patients with IBD in the United States.\(^22\)

ICN uses an actor-oriented network architecture\(^23\) to create a flexible and dynamic system to meet the needs of all participants and enable new levels of co-production of health care services.\(^24\) An actor-oriented architecture is an organizational form that enables large-scale self-organization and multi-party collaboration. The architecture consists of 1) actors who have the capabilities and values to self-organize, 2) a commons, where actors accumulate and share resources, and 3) protocols, structures, and processes that enable multi-actor collaboration.\(^23\) Commons-based peer production is a new model of socioeconomic production in which large numbers of people work cooperatively. Co-production means delivering services in a way that recognizes the reciprocal relationships between professionals, people using services, their families and their neighbors so that both services and neighborhoods become more effective agents of change.\(^25\)

In the ICN Network, all participants, patients, clinicians, researchers, collaborate to co-produce care, improvement, innovation and research (Figure 1). The framework for care management is the Chronic Care Model,\(^26{-}^{30}\) an evidence-based model of chronic illness care involving the use of patient registries for population management, pre-visit planning, decision support, promoting self-management, and auditing of care processes. Using formal innovation methods, ICN has developed: 1) a networked community of hundreds of individuals worldwide who contribute scores of innovations (e.g., technology for personalizing single case studies, peer-to-peer mentoring, online forum for patients and parents, crowd-sourced tools and resources posted on a virtual community commons; 2) micro-communities to maintain connections between participants; 3) community and leadership using formal community organizing methods and a governance structure with parents and patients in all key leadership positions; 4) formal research priorities by all
community stakeholders focused on information that patients and doctors need most, and 5) a registry where physicians capture data during clinical care and upload it, creating a ‘big data’ resource for effectiveness research and clinical trials, drastically reducing research costs.

The ICN registry collects data at each visit, with the idea that it goes in once and gets used multiple ways: for clinical care, quality improvement, and research (Figure 2). After joining the network, each site develops its own encounter forms that collect structured data required by the network. ICN supports quality improvement training and coaching to ensure the data are reliable. ICN created a Model Care Guideline (32) that includes details how to rate disease severity and accurately phenotype the disease according to a consensus guideline (33). Clinicians use the ICN registry for clinical care with automated pre-visit planning, where they are alerted if any of the standard guideline-recommended assessments are missing. It also allows clinicians to see a summary of all the patients they treat using automated population management.

Since it began, the percent of children in remission in ICN has increased from 60% to 81%, without new medications. The Network has deep patient and family leadership. Approximately 100 parents participate on quality improvement teams at participating centers and 5 of the 8 members of the ICN board of directors are parents. A team of youth with IBD, the ICN Patient Advisory Council, contribute to research studies and the development of health care innovations; they share valuable experiences with healthcare professionals, researchers and others; and they raise awareness of IBD and ICN via social media.

The ICN model is now being scaled up to create PEDSnet, as part of PCORI’s national research infrastructure transformation initiative called PCORnet.(34) PCORnet’s mission is to enable faster, more trustworthy clinical research that helps people make informed health decisions. The goal is to engage people, clinicians, and health system leaders in participating, create data sharing infrastructure, tools, and policies to support rapid, efficient clinical research and utilizes multiple data sources including electronic health records, insurance claims data, data reported directly by people, and other data sources. PEDSnet is a sub-group of PCORnet focused on children’s health. It includes 8 pediatric academic health centers. These have developed a national data, regulatory, scientific, and governance infrastructure to support research on acute, surgical, and chronic medical conditions in pediatrics.

**Pharmacology Studies**

There are several studies, completed and ongoing in the ICN network that have clinical pharmacology aims. An early ICN study examined data from 843 children with Crohn’s disease and 345 patients with ulcerative colitis.(35) Changes in care delivery that occurred after practices joined ICN were associated with an increase in the proportion of visits with complete disease classification, measurement of thiopurine methyltransferase (TPMT) activity before initiation of thiopurines, and patients receiving an initial thiopurine dose appropriate to their TPMT status. Adjusting thiopurine doses according to TPMT activity was only done in ~20% of the ulcerative colitis patients at the start of the study, and
improved to ~60% over the three years studied. Centers developed tools to support these changes in care, including: a population tracking and management tool; a Model IBD Care Guideline (32) emphasizing reduced use of prednisone and improved use of immunomodulators and biologic agents; previsit planning templates to ensure appropriate medication dosing (Figure 2), nutrition and growth classification, and laboratory monitoring; and flow diagrams to illustrate the use of protocols and auditing. The use of these tools reduced the unintended variation in the care of patients and produced significant increases in the proportion of patients with both Crohn’s disease and ulcerative colitis with inactive disease. This study demonstrates the power of a collaborative group to improve patient outcomes through standardized treatment regimens.

A second study by ICN researchers evaluated the effectiveness of anti-tumor necrosis factor-α (anti-TNFα) agents in the management of pediatric Crohn’s disease. (36) Previous studies on adult patients with Crohn’s disease demonstrated a benefit of anti-TNFα therapy versus placebo and thiopurines. (37) These same studies had not been done in children due to time, cost, and ethical (withholding an efficacious treatment) challenges. The ICN study analyzed data from more than 4000 patients with moderate to severe Crohn’s disease from 35 pediatric gastroenterology practices, and classified them as initiators or non-initiators of anti-TNFα therapy. During a 6 month follow-up period patients treated with anti-TNFα therapy had higher rates of clinical remission and corticosteroid-free remission. The authors concluded that anti-TNFα therapy was effective at achieving clinical and corticosteroid-free remission in Crohn’s disease patients treated in the routine pediatric gastroenterology practice setting. Utilization of the ICN network for this study allowed generalization of likely benefits to patients as it avoided very strict inclusion criteria that characterize explanatory clinical trials, which test efficacy and are not representative of real-world practice.

Currently, a randomized, double-blind, placebo-controlled, multicenter pragmatic clinical trial is being conducted to determine whether, in children with Crohn’s disease initiating anti-TNF biological therapy, low-dose oral methotrexate is more effective than placebo in the induction and subsequent maintenance of steroid-free remission. The primary outcome is the induction and maintenance of steroid-free remission. Secondary study endpoints include patient-reported outcomes (pain interference, fatigue, psychological stress experiences, and positive affect), indirect and direct markers of disease activity and mucosal inflammation and healing (including erythrocyte sedimentation rate, C reactive protein, albumin, and hemoglobin), and any adverse safety signals. This study, nicknamed COMBINE, has built in sample collection for pharmacology studies, of both methotrexate and anti-TNF therapies. Trials such as this are a great opportunity to incorporate clinical pharmacology. The registry collects all the information clinical and demographic information in a standardized way. The researcher can then request access to the samples and registry data by submitting a request form, proposal and data sharing expectations form to the ICN Research Committee. This will enable large-scale metabolomic, proteomic or genomic studies on the pathology, response to treatment, and the interaction between disease severity and treatment response (38). Biomarkers have been used as diagnostic tools, but less focus has been given to biomarkers predictive of response to therapeutics, an area of investigation that would benefit from large-scale metabolomic, proteomic, and genomic analyses (39). The efficacy of
different therapeutic options in individual subtypes of disease can be analyzed longitudinally within the network’s large cohort, which includes a consistent rating of disease phenotype and severity. Due to the learning structure of the network, these research findings can easily be translated into new treatment recommendations for specific subtypes in the future.

Case study

The ICN network empowers patients to be involved in their treatment, through advocacy, participation in their own care and the health care system, and research; the network also makes it easy for patients to be involved in clinical decision making. Recently, the parents of a 13 year old boy with Crohn’s disease approached a clinical pharmacologist not associated with the ICN network with the email below.

“Our son was diagnosed with Crohn’s last year and was started on Remicade. His trough level has frequently been sub-therapeutic. Our sense is there are multiple possible reasons for this but I imagined you would say most of them are avoidable with the right pharmacologic approach. Have you had any experience with Remicade (infliximab) for therapeutic monitoring? Seems like an area ripe for work given the cost of the drug and the risks of sub-therapeutic levels. We’d be curious about any thoughts you might have - that might help us and potentially the GI approach to Crohn’s. I’d be interested to meet if you think there are some opportunities to explore.”

Since the patient had access to the infliximab concentrations and dosing times through the ICN patient portal, the consult could be performed quickly. The infliximab doses and concentrations were modeled with clinical software (MW/Pharm, Mediware, Prague, Czech Republic) using Bayesian estimation with a pediatric population model as the prior (40) in a similar fashion as recently described for adult patients with Crohn’s disease. (41, 42) Individual infliximab pharmacokinetic estimates were based on the three most recent concentration measurements (2 pre-dose and an 18 days post-dose concentration result). Based on a pre-dose target concentration range of 3–7 mg/L, three different dosing regimens were generated (300, 500 or 700 mg) for target attainment (Figure 3A). The patient’s parents contacted the physician with this recommendation, who agreed to change the dosing regimen based on the predictions. A follow up concentration was measured 8 weeks after the adjusted dosing regimen was implemented, however, was still below the desired target concentration. When this observation was included in the model, a shortening of the dosing interval from 8 to 6 weeks was predicted to result in the desired concentration of around 7 mg/L (Figure 3B). This case example generated great enthusiasm and interest from parents, patients and providers to further explore the potential of model based precision dosing as an additional dynamic intervention in the setting of a learning network.

Vision for the future

Our vision for the future is a drug dosing dashboard that will be used to improve the dosing of biologics to treat Crohn’s disease. Current evidence suggests that pharmacokinetically guided precision dosing of anti-TNF-α (tumor necrosis factor alpha) monoclonal antibodies (mAbs) has great promise as it may result in better disease control in inflammatory disease.
In a recent review and commentary in this journal, Mould et al. provide a comprehensive overview of PK/PD model-based dosing guidance highlighting the evolution of decision support tools, including Bayesian systems. The described dashboard decision support platform offers unique advantages over simpler dose calculators in terms of the ability to integrate all available patient information to individualize therapy. Appreciation of each patient’s unique clinical and PK/PD characteristics warrants a tailored approach particularly in case of patients with high disease activity who are at increased risk for underexposure and treatment failure. However, implementation of decision support systems is a complex process that requires a true multidisciplinary endeavor. And although several dashboards have been described and prospectively evaluated much work remains to be done to accomplish interfacing of clinical and PK/PD dashboard systems with Electronic Health Records. A Learning Health System, such as the ICN network described here, represents an ideal environment to facilitate such implementation as it already harness the power of the electronic medical record, engages patients, families and clinicians, and fosters research of novel interventions across participating institutions which ultimately will inform best practices.

In an effort to better understand the number of patients that could benefit from personalized dosing regimens for infliximab, data from the ICN registry are currently being evaluated to address several basic questions that could provide important insights in the current patient management status: e.g. what is the distribution of infliximab levels throughout the network?; and is there an actionable association between infliximab exposure and antidrug antibody and albumin levels as suggested in several studies? Given the highly variable pharmacokinetics of infliximab, a significant number of pediatric patients could be well below or above the identified target concentrations as they were in trials of adults and small pediatric studies. Another interesting question that can be answered with these data is whether the rather empirically established therapeutic target would be adequate for all patients, or whether some would benefit from an individualized exposure-response target. Once these questions are answered, a decision support tool can be developed to help all patients reach his/her own therapeutic optimum, which can then be incorporated automatically into the pre-visit planning tool. This tool could be rolled out to the entire network very quickly. The example further illustrates how a Learning Health System can be used to provide the tools and resources to make progress towards precision medicine and how to accelerate the practice and application of personalized medicine in real-world clinical environments. There is even greater potential to improve the remission rate further than has already been accomplished through the network standardization efforts.

Finally, this effort could be expanded to include other medications used and related diseases as well. The dashboard would take into account the concentration of the medication in the blood and clinical characteristics (age, weight, albumin concentration, antibody concentration, time since last dose) and use pharmacokinetic modeling to predict a dose that would provide the patient his/her personalized therapeutic concentration. By including it in a learning health system where the patients are actively engaged and there is an app to track symptoms, efficacy, and quality of life, the dashboard could also be a learning system, improving the model “under the hood” with each additional measurement.
Once developed for a specific medication and disease, such as biologics in Crohn’s disease, the drug dosing dashboard could be adapted for more medications and more diseases, especially where these same medications are used (arthritis, psoriasis, etc). For example, many of these patients also receive methotrexate. Genetic variants and clinical characteristics that predict clearance of methotrexate in oncology patients are well-described, but have not been studied thoroughly in CD patients. Methotrexate has been shown to decrease the immunogenicity of mAbs such as infliximab (51). With the COMBINE study already ongoing within the ICN network, we are poised to study how the two medications interact, and develop predictors of response (clinical characteristics, adherence, metabolites, genetic variants, etc). With a dashboard that could take into account clinical characteristics, genetic variants, infliximab concentrations, anti-infliximab antibodies, and methotrexate use in a user-friendly interface, clinicians could more easily understand the risk for toxicity or under-treatment and adjust the doses of each medication accordingly, realizing the goal of precision medicine.

Acknowledgments

We would like to acknowledge the patients, families, clinicians, researchers and staff who participate in the ImproveCareNow Network for their tireless contributions to improving the health of children with Crohn’s Disease and Ulcerative Colitis. We are thankful to Pamela J. Schoettker for medical writing assistance.

Disclosure: Research funding has been received from the NIH NIDDK R01DK085719, AHRQ R01HS020024, AHRQ U18HS016957, PCORI PPRN-1306-01754, ImproveCareNow Network Care Centers, and the CCHMC Learning Networks Program.

References


Figure 1. Improving Outcomes with a Learning Health System

The diagram illustrates information flow through a Learning Health System. Patients and clinicians interact. Data that result from their interaction is captured electronically and fed back into the system to be used for quality improvement and measurement of outcomes. Information about process and outcomes is used to identify gaps in care and to understand variation in outcomes. This information is used by groups of participants, patients, clinicians and researchers, to identify high priority questions to inform research. This resulting evidence and knowledge is then fed back into care. When the learning cycle is fully operational, research influences practice and practice influences research. All stakeholders are involved in this learning health system, working together to create new knowledge that influences best practices at the point of care and aims to improve patient outcomes.
### IBD PRE-VISIT ASSESSMENT – INDETERMINATE COLITIS

| Diagnosis: Indeterminate Colitis - 1/2011 | Last Visit: 3/19/2015 | Last PPD & Date: Not Recorded |
| Phenotype: Inflammatory, non-penetrating, non-structuring | WT (kg): 55.85 | Last CXR: Not Recorded |
| Lower: Colonic only | HT (cm): 174.80 | |
| Upper Proximal: No | BSA: 1.647 | |
| Upper Distal: No | Date of last hospitalization: 12/6/2014 | Last Gold Test & Date: Negative 5/6/2014 |
| Perianal Phenotype: No |

#### Visits:

<table>
<thead>
<tr>
<th>05/01/2014</th>
<th>07/01/2014</th>
<th>08/14/2014</th>
<th>09/18/2014</th>
<th>10/30/2014</th>
<th>12/04/2014</th>
<th>01/22/2015</th>
<th>03/19/2015</th>
<th>Age of Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGA Quiescent</td>
<td>Quiescent</td>
<td>Mild</td>
<td>Quiescent</td>
<td>Quiescent</td>
<td>Quiescent</td>
<td>Quiescent</td>
<td>Quiescent</td>
<td>Quiescent</td>
</tr>
<tr>
<td>Nutritional Status Satisfactory</td>
<td>Satisfactory</td>
<td>Satisfactory</td>
<td>Satisfactory</td>
<td>Satisfactory</td>
<td>Satisfactory</td>
<td>Satisfactory</td>
<td>Satisfactory</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>Growth Status Satisfactory</td>
<td>Satisfactory</td>
<td>Satisfactory</td>
<td>Satisfactory</td>
<td>Satisfactory</td>
<td>Satisfactory</td>
<td>Satisfactory</td>
<td>Satisfactory</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>Albumin 4.6</td>
<td>4.1</td>
<td>4.1</td>
<td>3.9</td>
<td>4.2</td>
<td>4.2</td>
<td>4.2</td>
<td>6 mo</td>
<td>6 mo</td>
</tr>
<tr>
<td>CRP 1.50</td>
<td>0.50</td>
<td>3.00</td>
<td>1.20</td>
<td>1.20</td>
<td>1.00</td>
<td>1.30</td>
<td>1.30</td>
<td>1.30</td>
</tr>
<tr>
<td>ESR 2.0</td>
<td>7.0</td>
<td>8.0</td>
<td>9.0</td>
<td>10.0</td>
<td>6.0</td>
<td>10.0</td>
<td>37.0</td>
<td>37.0</td>
</tr>
<tr>
<td>Hematocrit 41.0</td>
<td>36.6</td>
<td>37.0</td>
<td>39.4</td>
<td>40.5</td>
<td>39.1</td>
<td>37.2</td>
<td>38.9</td>
<td>38.9</td>
</tr>
</tbody>
</table>

*Result date may differ from visit date

1. Lab ordering guidelines: S-ASA, q4mo
2. ESR q3mo
3. Hemoglobin q2-3mo

#### Care Stratification

<table>
<thead>
<tr>
<th>CS Score</th>
<th>CSS Group</th>
<th>Current Disease Activity</th>
<th>12 Month Disease Activity</th>
<th>BMI Z-Score</th>
<th>HT Velocity</th>
<th>Hosp Adm within 3 months</th>
<th>Currently on Cortico</th>
<th>Cortico last 12 months</th>
<th>Psychosocial Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.3 (Low)</td>
<td>0 (Quiescent)</td>
<td>0 (Quiescent)</td>
<td>0 (BMI/Z-Score =&lt; 1 or Missing)</td>
<td>0 (No or Unknown)</td>
<td>0 (Infectious)</td>
<td>0 (No or Unknown)</td>
<td>0 (No or Unknown)</td>
<td>1 (Yes)</td>
</tr>
</tbody>
</table>

#### Treatments

<table>
<thead>
<tr>
<th>Thalidomide/TPMT</th>
<th>Dose (mg)</th>
<th>mg/kg (last wt)</th>
<th>Guideline</th>
<th>Attention Needed</th>
</tr>
</thead>
</table>

#### Immunomodulators

| Thiopurines TPMT | Normal/high (4/11/2011) | Consideration: If active BS, consider LTOT levels q 90 |

#### Biologics

| Adalimumab/Nimura | 40.0 | 0.7 |

#### Other Labs

<table>
<thead>
<tr>
<th>Levels</th>
<th>Dates</th>
<th>Levels</th>
<th>Dates</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>6AMP</td>
<td>6-TGN: 332.0</td>
<td>7/7/2013</td>
<td>6AMP: 3075.0</td>
<td>7/7/2013</td>
</tr>
</tbody>
</table>

#### Considerations:

- **CSC:** Consider an order for Hematocrit. Patient on biologics and date of last result more than 60 days ago.
- **CSR:** Consider an order for CSR. Patient on biologics and date of last result more than 60 days ago.
- **CPR:** Consider an order for CPR. Patient on biologics and date of last result more than 60 days ago.

- **Albumin:** Consider an order for Albumin. Patient on biologics and date of last result more than 60 days ago.

### Additional considerations for patients in REMISSION:

- Consider careful assessment of medication adherence
- Review health maintenance issues such as annual eye exams, stool checker, immunizations, psychosocial functioning, transition of care, etc. as indicated
- Review self-management techniques

#### Disclaimer:

Unless specifically entered by your center, this report does not contain information for events that occur outside of the clinic visit.

---

*Clin PharmacoTher. Author manuscript; available in PMC 2018 March 01.*
Figure 2. Pre-visit Plan Example

A. The automated pre-visit assessment alerts the clinician if any of the standard guideline-recommended assessments are missing. Dosing recommendations for thiopurines based on TPMT status and thioguanine nucleotides (TGNs, active drug metabolites) are provided to the clinician. B. The pre-visit planning tool also includes a longitudinal graph of the patient’s nutritional status (purple), physician’s global assessment (PGA, maroon), and Short Pediatric Crohn’s Disease Activity Index (SPCDAI, brown) plotted over time in conjunction with the medications and labs below. CRP, C-reactive protein. ESR, erythrocyte sedimentation rate.
Figure 3. Pharmacokinetic model-based prediction of infliximab concentration
Panel A: Predicted infliximab concentration-time profile (green line) based on patient demographics, dosing history and the 3 most recent measured concentrations (3.9, 11.0 and 30.0 mg/L; open circles) using Bayesian estimation. Based on the individual pharmacokinetic (PK) parameter estimates, three different dosing scenarios were simulated: 700 mg every 8 weeks (red line) would achieve a pre-dose trough concentration of 7 mg/L (upper dotted line); 500 mg every 8 weeks (dark blue line) to achieve a trough target of 5 mg/L; and 300 mg every 8 weeks (light blue line) that would result in a trough concentration
of 3 mg/L (lower dotted line). Panel B: updated PK profile (orange line) based on the follow up measurement of 2.1 mg/L followed by a dose adjustment to 500 mg every 6 weeks. The next concentrations measured, one random mid-interval and one pre-dose concentration (25.0 and 7.9 mg/L, respectively) are in line with the model prediction and indicate target attainment (open circles).