Pediatric Ethicscope is a biannual peer-reviewed journal dedicated to pediatric bioethics and clinical ethics. The Journal accepts manuscripts on these and related subjects through our online submittal process. The journal is open access to readers, and does not charge authors any fees for publication. Pediatric Ethicscope is supported by the Children's National Health System. Please visit our website for more information about the manuscript submittal and peer-review process.

For Once, Then, Something

Others taunt me with having knelt at well-curbs
Always wrong to the light, so never seeing
Deeper down in the well than where the water
Gives me back in a shining surface picture
Me myself in the summer heaven godlike
Looking out of a wreath of fern and cloud puffs.
Once, when trying with chin against a well-curb,
I discerned, as I thought, beyond the picture,
Through the picture, a something white, uncertain,
Something more of the depths—and then I lost it.
Water came to rebuke the too clear water.
One drop fell from a fern, and lo, a ripple
Shook whatever it was lay there at bottom,
Blurred it, blotted it out. What was that whiteness?
Truth? A pebble of quartz? For once, then, something.

—Robert Frost
Unpleasant choices are intrinsic to the problem of medical lifesaving therapy selection; they are the very essence of the matter.

– Nicholas Rescher (1969)
Shortages: The New Normal in Pharmacy
Radha Rohatgi, PharmD, BCOP, Devona Williams, PharmD, BCOP, Tim Harrison, CPHT, Eds.

What Lies Beneath: The conflicting principles underlying the drug shortage crisis
Stowe Locke Teti

From Classroom to Clinic: Fighting to Meet the Obligation to Treat the Whole Patient
Joseph Bokum Lee, MD, MAT

Education in Ethics
Harvard Medical School Center for Bioethics Clinical Bioethics Course
Stowe Locke Teti, Executive Editor
Ethicscope Editorial Group

Ethics in the Pediatric Literature
Tomas Silber MD, MASS
With this issue, a decades-old dream has become real. Pediatric Ethicscope has been published as a newsletter since 1987; it is arguably the first, if not only, continuously produced publication devoted to pediatric ethics, and one that stood witness to the development of the field of bioethics itself. Pediatric Ethicscope was the brainchild of Dr Sanford Leikin, one of the pioneers of the field of Pediatric Ethics, who served as its first Editor-in-Chief. Jacqueline Glover PhD took the reigns in the nineties, and Tomas Silber, MD, MASS has continued that tradition since the turn of the new century. Pediatric Ethicscope is now entering its 30th volume; it has, and will continue, to present the work of multidisciplinary contributors sharing diverse and nuanced perspectives on issues of import to pediatric medical ethics. Our aim is to disseminate the best and latest thinking on pediatric ethics.

Many Journals are now devoted to the exploration and dissemination of bioethical knowledge. Our interest, pediatric ethics, has by now developed a vast field of knowledge that made clear that pediatric ethics isn't just an adaptation, a “smaller size bioethics”, rather in many ways, it is quite different, and sometimes significantly more complicated. The movement from bilateral clinical relations between patient and clinician to trilateral relations involving minor patients, family, and clinicians, presents myriad complications, and the issues, seemingly comparable, are frequently quite distinct: “end of life” issues occurring at birth or soon after, invoke a set of concerns altogether different than those we have for our parents and grandparents.

These dynamics justify the increasing number of articles in the field and contribute to the need for a peer-reviewed journal dedicated to pediatric bioethics. Tomas Silber MD envisioned such a project nearly a decade ago. However, at that time Pediatric Ethicscope was not ready for prime time; though many articles were extremely interesting and moving, there was no external peer-review process, no editorial board, no published guidelines for authors, nor any of a number of matters necessary for a journal to function beyond the walls of a single institution and be accepted by the clinical and academic community it seeks to serve.

So, we started building. After years of planning and preparation, we are ready to enter the fray. And while we have created the aforementioned mechanisms requisite of a rigorous and professional journal, a larger task lies ahead. This project succeeds or fails on the quality and volume of manuscripts we receive, and number of readers we attract; in other words, this project succeeds or fails with you.

The journal and its editors endorse and subscribe to the best, and most stringent, journal publishing practices—those, and our operational Policies, Procedures, and Guidelines are published on our website, which we encourage you to visit. A word about our sponsorship: while we are supported by Children’s National Health System (CNHS), we are editorially independent. In that spirit CNHS has supported the creation of an entirely independent website for Pediatric Ethicscope. We also have the benefit of an Editorial Board whose members need no introduction (see pages 6-7). We are humbled...
by their support of this project and their generous donation of time.

We will continue the tradition started by Dr. Leikin, including two distinguished features: a rendition of the annual Leikin Lecture in Pediatric Grand Rounds at Children’s National, and a winning article of the annual Pediatric Ethicscope Essay Contest for new authors (See page ). Our staff is available to discuss your ideas and make suggestions prior to the formal review process. This can save you time, and get you on the right track. We urge first-time authors to contact us to take advantage of this opportunity.

Finally, we would like to invite all of our readers to both return feedback, and spread the word. Let us know what you like or dislike, for our project is a dialogue. We look forward to your response, and hope you will join us.

Tomas Jose Silber MD, MASS, Editor-in-Chief of Pediatric Ethicscope, is Director of the Pediatric Ethics Program at Children’s National Health System, where he leads the Clinical Ethics Consult Service and Chairs the Clinical Ethics Committee. Dr. Silber is the Ethicist at the Children’s National Clinical Translational Science Institute, where he serves on the leadership committee and as the Research Subject Advocate. Dr. Silber is an Adolescent Medicine specialist with over 50 years of experience who has written extensively on pediatric ethics, including work on the American Academy of Pediatrics Bioethics Resident Curriculum. Dr. Silber is a former Chair of the American Academy of Pediatrics Section of Bioethics, and long-continuing mentor to many in the bioethics community.

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Shortages of Drugs, Surpluses of Ethical Challenges
An Allocation Framework for Childhood Cancer

Yoram Unguru, MD, MS, MA

“Unpleasant choices are intrinsic to the problem of medical lifesaving therapy selection; they are the very essence of the matter.”

– Nicholas Rescher (1969) [1]

Shortages of life-saving chemotherapeutics and supportive care agents are pervasive and enduring. These shortages represent a true public health crisis, and surprisingly, have failed to garner greater attention within the medical community or the public at-large. In the United States, shortages of drugs, including chemotherapy and supportive care agents, have become a “new normal.”

Shortages of medications and essential medical resources have a long-standing history and provide an important perspective when examining current
scarities of life-saving chemotherapy and supportive care agents. One of the first large scale drug shortages in the early 1920s involved insulin [2] and was followed in the 1940s by shortages of penicillin, which affected far greater numbers of patients [3]. In the 1960s, the medical community grappled with shortages of dialysis machines [4].

More recently, clinicians and patients have experienced shortages of seasonal influenza and H1N1 influenza vaccines. Perhaps one of the most enduring US shortages is organs for transplantation, with over 120,000 Americans in need of an organ at the time of this writing [5]. Many U.S. hospitals lack adequate health care providers, as evidenced by the dearth of skilled nurses [6], while recent natural disasters such as Hurricane Katrina [7], and infectious disease outbreaks like Ebola, [8] highlight the difficulty of identifying practitioners willing to provide care in these situations.

Shortages of insulin, penicillin, and dialysis machines are especially instructive when considering the method by which each was ultimately allocated. Like many current drug scarcities, both insulin and penicillin shortages were the result of an inability to manufacture adequate supply, while scarcity of dialysis machines was the result of limited financial resources to pay for the therapy.

Dr. Frederick Banting, one of the discoverers of insulin, was responsible for its prioritization. Banting’s allocation decisions were often biased and arbitrary and were influenced by “emotional, political, and personal appeals,” such that acquaintances and the politically well-connected received priority over others [9]. Penicillin shortages occurred during the height of the Second World War. The decision to preferentially allocate penicillin to US soldiers and not civilians was made by the Committee on Chemotherapeutic and Other Agents [3]. This decision was made without stakeholder engagement and caused an outcry among the larger public who disagreed with the decision-making rationing process and with the failure to disclose the criteria for patient selection.

Decisions about allocating dialysis were determined by a 7-member panel that has become known as the “Seattle God Committee” or “God Squad” [10]. In addition to relying on medical criteria such as, prognosis and health status, the committee assigned priority based on social worth; churchgoers and those with dependents (i.e., parents) received priority allocation over non-church-goers and non-parents. Each of these examples sheds light on the limitations associated with individual and committee-based allocation of life-saving medications and emphasizes the importance of a transparent and public prioritization process.

The Problem
Over the past 10+ years, drug shortages have become increasingly commonplace. Chemotherapy (and supportive care) agents are particularly prone to scarcity and are consistently ranked among the top 5 drug classes in short supply. Like many of the drugs that are in short supply, most affected chemotherapy agents belong to the class of older, generic, sterile “injectables.” In fact, since 2001, between 50%-75% of all drugs on the US “short list” are sterile injectables. As most chemotherapy is administered via injection, oncology practices are disproportionately affected by the shortage. Injectables largely comprise the backbone of proven and standard life-saving regimens for children and adults and children with cancer are particularly vulnerable, as there exist few, if any alternative agents.

The reasons for drug shortages are complex and are especially common in the USA (see Figure 1); [11-16] economies of scale, limited profit margins, quality failures, consolidation in the marketplace, a lack of manufacturing redundancy, inadequate
market competition to drive down prices, regulatory considerations, and the federal government’s inability to negotiate drug prices all contribute to shortages.

Compelling research examining the economic drivers and business decisions that contribute to US drug shortages raises serious concerns. The generic chemotherapy market has become consolidated with merging of suppliers and outsourcing of drug components. As drug manufacturers often contract other companies to make their drugs, it is not publicly known who makes what for whom so there is no way to truly know what the supply chain is and no publicly available data on which manufacturers farm-out drug production. As recently demonstrated, having fewer chemotherapy drug suppliers is associated with a higher likelihood of shortages. Moreover, the strongest risk factor for a shortage is the age of the drug, with older drugs significantly more likely to experience shortages [16]. This is particularly concerning as the majority of chemotherapy agents used to treat, and to cure, most childhood cancers are older drugs. A case in point, childhood acute lymphoblastic leukemia or ALL is the most common childhood cancer accounting for nearly one-quarter of all children diagnosed with cancer with a survival rate approximating 90%. The overwhelming majority of drugs used to treat and cure ALL have been in use for more than 50 years and over the past decade, 8 out of 10 common drugs used in the treatment of ALL, have temporarily been unavailable.

As recently reported, availability of generic drugs and chemotherapeutics in particular, is directly linked to decisions by manufacturers that either delay or prevent these drugs from becoming accessible. Such decisions are associated with considerable cost absorbed by patients, governments, and insurance companies that results in increased revenues for brand-name drug companies, prompting at least one influential group to conclude that the dual mission of helping patients while simultaneously profiting has been replaced by “a mission to make profits at any cost.” [17]

Scope of the problem
According to data from the American Society of Health Systems Pharmacists, which monitors US drug shortages [18], drug shortages reached an all-time high in the fall of 2014, with 320 shortages. In 2015, there were 142 new drug shortages with 185 active drug shortages in the final quarter of 2015. In other words, although there were fewer new drugs in short supply, because of an inability to resolve existing shortages, the total number of active shortages remained high.

With regard to chemotherapeutics, at the end of 2015, 13 chemotherapy agents were in short supply, fewer than previous quarters and less than the record 33 chemotherapy agents that were in short supply at the end of 2013. Patients receiving chemotherapy typically require more than a single chemotherapeutic. Being able to administer a chemotherapy agent that was previously scarce does little if other chemotherapy agents used as part of the same (curative) regimen are lacking. Similarly, without the critical supportive care agents, patients with cancer rely upon, e.g., leucovorin, corticosteroids, anti-emetics, and intravenous fluid solutions, all of which have been, or currently are in scarcity, administering chemotherapy is unsafe, ill-advised, unpleasant, and even impossible.

Although fewer chemotherapy shortages is certainly “good news,” drug shortages are not isolated strictly to chemotherapeutics or to a particular drug class. Shortages occur across drug classes and have far reaching consequences. With shortages of central nervous system drugs, antibiotics, electrolytes and minerals, critical care and cardiac drugs, and even normal saline (salt water), shortages impact most patients and physicians.

Consequences
The consequences of drug shortages are far-reaching. The annual costs associated with managing drug shortages has been estimated to be $416 million [19]. Beyond the economic costs associated with drug shortages, drug shortages directly impact patients’ lives and this is especially true for children with cancer. Drug shortages in general and shortages of CASCA specifically, result in increased medication errors,
delayed administration of life-saving therapy, inferior outcomes, and patient deaths [20-25].

In 2009, the chemotherapeutic, mechlorethamine, approved for use in the US in 1949 and included as part of multiagent chemotherapy regimens for the treatment of Hodgkin lymphoma for over 50 years became unavailable due to a shortage. At the time of the mechlorethamine shortage, evidenced suggested that another chemotherapeutic - cyclophosphamide - could be safely substituted for mechlorethamine to treat certain pediatric patients with Hodgkin lymphoma. However, as reported by Metzger and colleagues [22], the 2-year event-free survival for 40 patients who received the alternative regimen with cyclophosphamide, was 12.5% lower than patients who had received the standard of care treatment including mechlorethamine. The authors note that while there were no deaths at the time of their analysis, patients who received cyclophosphamide received additional rounds of toxic chemotherapy, including stem cell transplantation, the long-term consequences of which remain unknown.

A recent survey of principal investigators (PI) and pharmacists at Children’s Oncology Group (COG) affiliated centers assessed the impact of chemotherapy shortages over a 2-year period on clinical trials (both COG and non-COG trials) and patient care. Fifty percent of COG PIs reported that at least one patient they cared for who was enrolled on a clinical trial was affected by the shortages and 66% reported that at least 1 patient’s clinical care was affected by the shortages. Equally troubling, 34% of pharmacists reported at least 1 near miss or actual medication error due to the shortages [25]. Shortages of chemotherapy however, are not isolated to children. With over 1.6 million US adults diagnosed with cancer each year (compared to fewer than 15,000 children), older patients are especially at-risk. Two surveys of medical oncologists assessed the impact of the chemotherapy shortages and lend insight to the severity of the problem. Nearly 83% of oncologists reported they were unable to prescribe their preferred chemotherapy agent; more than 75% had to make a major change in treatment such as choosing a different treatment regimen or substitute different drugs during treatment; over 40% were forced to delay the start of treatment; and 28% reported using a less-effective alternative because of a shortage [24,26]. Perhaps most concerning was the fact that nearly 70% of oncologists reported that their hospital or practice lacked any type of formal guidance for how to make decisions about allocating drugs, prompting the authors of the study to appropriately call for formal guidance in this regard.

Event-free survival (EFS): original Stanford V regimen with Mechlorethamine compared with modified Stanford V Regimen with Cyclophosphamide for Hodgkin’s Lymphoma patients. Two-year EFS was 75% among patients who received cyclophosphamide (SE, 12.5%) and 88% among those who received mechlorethamine (SE, 2.5%; P = 0.01).


Ultimately, drug shortages prevent clinicians from providing a reasonable standard of care and they hinder critical clinical research that is essential to guarantee ongoing advances in understanding disease processes and improving outcomes.

**Ethics questions**

Drug shortages present a host of ethical challenges for patients, providers, and healthcare systems. Should providers delay treatment, administer a lower dose of a medication, or skip a dose altogether? Should patients be prioritized, and if so, is the bedside treating physician or an independent neutral panel best suited to make these decisions? Should children receive priority over adults? Is it appropriate to allocate a scarce medication according to patient size, weight or developmental status? Should patients enrolled on a clinical trial receive preferential access to a scarce drug over those who opt not to participate in these trials? If allocation is deemed appropriate, what prioritization model should be relied upon? If scarce drugs are available outside approved and legal channels, through the so-called gray market, should hospitals, providers, and patients access them knowing that this practice may exacerbate shortages and that the

"Faced with prioritization, allocation decisions must be reasoned, explicit, transparent, and public."
pedigree of the drugs obtained via the gray market is not guaranteed?

**To prioritize or not to prioritize**
Solving the drug shortage problem will ultimately require a concerted, coordinated, and cooperative effort with broad stakeholder engagement including members of government, industry, professional organizations, and patient advocates. Until such a time comes, as a society, we must be prepared to make difficult decisions about allocating scarce life-saving chemotherapy among equally deserving children.

Although prioritization of scarce health care resources is viewed by many outside the US as acceptable, necessary, and even ethical, prioritization has yet to gain wide spread support among large portions of the American public. Opponents have been quick to equate prioritization with “rationing,” and in some circles, prioritization has been framed as, “death panels.” [27] Yet rationing occurs frequently in the American health care system. Insurance companies ration when deciding which medications to include on their formularies, transplantation organizations ration when deciding how to allocate organs, and hospitals and other clinical groups assign priority access to vaccines. Moreover, a broad group of American scholars and policy experts, favor allocation as both necessary and morally permissible [28].

Irrespective of one’s position, the unrelenting shortages of life-saving medications accompanied by providers’ pleas for guidance mandates an ethical approach towards allocation of critical and essential medications. Yet, being forced to ration life-saving chemotherapeutics and supportive care agents raises serious ethical concerns. How then should providers proceed?

Bedside rationing is problematic and ill suited for such a decision-making process. Bedside rationing is prone to subjective preferences and arbitrary decision-making and fails to treat similar people similarly and in so doing, violates the ethical principle of justice [29]. Other approaches towards allocation include such models as, first-come first-serve, chance-based allocation (i.e., lottery), and prioritization based on medical urgency or social value criteria according to the patient’s perceived value to society.

Although allocation decisions can certainly be made conforming to anyone of these approaches, each has strengths and weaknesses and on its own is insufficient. While clinicians may combine various features of each when choosing to allocate a scarce resource, this may prove difficult in practice. Ultimately, none of these frameworks readily provides concrete guidance clinicians desire when faced with making difficult prioritization decisions among equally deserving children with cancer. What is required is an overarching framework that can be equally and fairly applied to all patients.

**Allocation Process**
Although ethical allocation of life-saving chemotherapy (and other medications) should include the clinician’s input, actual decision-making must not occur at the bedside and is better suited to be performed by a diverse independent panel.

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**Mitigation Strategies to Maximize Efficiency and Minimize Waste**

1. Verify whether ASHP or FDA list the drug as scarce
2. Obtain an update on shortage supply and likely duration
3. Anticipate drug needs for current and expectant patients
4. If the preferred drug brand or strength is not available, contact manufacturers directly as alternate product sizes (i.e., larger or smaller vial size) may be available
5. Cohort patients receiving similar therapies to share vials otherwise meant for single-use
6. If applicable, select an alternative therapy
7. Borrow and share drug(s) with neighboring institutions
8. Alternate dosing (lower/less frequent if appropriate)
9. If scarcity is to be short-lived, give drug out of sequence
10. Skip a dose
11. If feasible, compound drug on own or acquire from a commercial compounding pharmacy
12. Acquire scarce drug via FDA from a non-US supplier
13. If stability/sterility profile supports doing so, consider extending drug usage beyond typical and accepted practice
Given the problematic nature of bedside allocation decision-making, prioritization decisions should be made by a multidisciplinary institutional Drug Shortage Committee or similarly appointed body with appropriate stakeholder representation (e.g., Pharmacy and Therapeutics Committee, Ethics Committee).

To address this issue, a 7-member interdisciplinary and multi-institutional Allocation Task Force (TF) with expertise in pediatric oncology, bioethics, nursing, patient advocacy, psychiatry, research ethics, palliative care, pharmacy, and pharmacology was convened to create an ethical and defensible allocation framework.

Functioning as a hypothetical drug shortage committee, the TF reached consensus on an ethical framework, which delineates a process for actual rationing of life-saving chemotherapy and supportive care agents. In establishing its framework, the TF considered the various existing allocation schema and emphasized a consistent approach grounded upon ethical, legal, and socio-cultural considerations.

Our guidance [30] represents a systematic recommendation aimed to minimize bias as might occur when individual clinicians or institutions are forced to make bedside rationing and prioritization decisions.

Ideally, decisions about allocating a particular drug in a given circumstance should be supported by evidence-based recommendations, yet such guidance to choose one patient over another rarely exists. Our framework provides an approach to these challenging situations. Importantly, it will serve to alleviate some of the tension individual clinicians may feel when confronted with having to make bedside decisions that can be inefficient, uncomfortable, prone to subjective preferences, and (understandably) reliant upon clinicians’ primary obligation of beneficence.

An independent panel of peer-consultants with expertise in pediatric oncology, law, regulatory affairs, pharmacology, bioethics, and advocacy reviewed a preliminary version of the report. The consultants’ feedback was incorporated into a revised report. The final report, endorsed by the leadership of the Children’s Oncology Group (COG) and the American Society of Pediatric Hematology/Oncology, provides reasoning for explicit decision-making in the face of an actual drug shortage and specifically aims to assist COG member-institutions navigate this difficult decision-making process.

The Framework

Faced with a drug shortage, the TF recommends a 2-step process. Step 1 includes strategies to mitigate an existing shortage based upon maximizing efficiency and minimizing waste. Step 2 elucidates actual prioritization (across and within diseases) grounded upon a modified utilitarian model that maximizes benefit according to total lives saved / life-years saved.

### Allocation considerations during chemotherapy and supportive care agent shortages.

<table>
<thead>
<tr>
<th>Guiding principle</th>
<th>Chemotherapeutic</th>
<th>Representative disease</th>
<th>Allocation rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug allocation should be evidence-based</td>
<td>Methotrexate</td>
<td>ALL, NHL, Osteosarcoma</td>
<td>Based on the strength of evidence, pts. w/ALL &amp; NHL should receive priority over those w/osteosarcoma IT-MTX &gt;&gt; Systemic MTX</td>
</tr>
<tr>
<td>Maximize benefit according to total lives saved / life-years saved</td>
<td>Methotrexate</td>
<td>ALL, NHL</td>
<td>Escalating dose Capizzi regimen &gt;&gt; superior HD-MTX</td>
</tr>
<tr>
<td>Incremental importance of a particular drug to a given pt.’s prognosis, including diseases w/poor prognosis</td>
<td>Doxorubicin, Cisplatin, Vincristine</td>
<td>Sarcomas, GCT, Marcy</td>
<td>Prognoses notwithstanding, each drug has a crucial role in offering the chance for cure</td>
</tr>
<tr>
<td>Total amount of the scarce drug required per regimen</td>
<td>Dactinomycin</td>
<td>Wilms tumor (low-risk)</td>
<td>WT is curable requiring a relatively small amount of the scarce drug</td>
</tr>
<tr>
<td>Phase of therapy</td>
<td>Vincristine</td>
<td>ALL, NHL</td>
<td>Patients w/larger disease-burden, early-on in the course of treatment, should receive priority</td>
</tr>
<tr>
<td>Anticipate drug needs, allocating drug(s) for current and expectant patients (so-called, rainy-day fund)</td>
<td>Leucovorin, Pegaspargase</td>
<td>Osteosarcoma, ALL, ALL</td>
<td>Each drug is considered “high-priority,” e.g., leucovorin for pts. receiving MTX; VCR for pts. w/ALL receiving induction; PEG-Asp for patients w/ALL</td>
</tr>
</tbody>
</table>

ALL = acute lymphoblastic leukemia; GCT = germ cell tumor; NHL = non-Hodgkin’s lymphoma; RMS = rhabdomyosarcoma; WT = Wilms tumor. HD-MTX = high-dose methotrexate; IT-MTX = intrathecal methotrexate; MTX = methotrexate
Select examples of mitigation strategies include the following:

- Drug shortages should be viewed as a public health crisis. Not only will this result in greater public awareness, it also provides a mechanism for potential remediation.
- Hospitals should not order more drug than they typically require in a given period, i.e., hospitals should not hoard drugs.
- Drug manufacturers and distributors may serve as “gatekeepers,” internally allocating drugs by verifying a hospital’s ordering history.
- Hospitals that lack a drug required by a patient should attempt to secure a supply for that patient from another institution or refer the patient to another institution able to provide the necessary care.
- Patients receiving similar therapies should be brought to the hospital/clinic on the same day to share vials that are otherwise meant for single-use.
- If the preferred drug brand or strength is not available, contact manufacturers directly as alternate product sizes (i.e., larger or smaller vial size) may be available.
- If appropriate, an alternate dosing approach should be administered (e.g., lower or less frequent dose).
- If scarcity is expected to be short-lived, the scarce drug should be administered out of sequence.
- If feasible, compound drug on own or acquire from a commercial compounding pharmacy.
- When US drug manufacturers are unable to address a shortage in an expedient and timely manner, FDA should investigate the feasibility of securing an adequate supply of the drug from a non-US supplier until the shortage has been alleviated.
- If stability and sterility profile supports doing so, consider extending drug usage beyond typical and accepted practice (i.e., administer an expired drug).

Faced with prioritization, allocation decisions must be reasoned, explicit, transparent and public. Such accountability is more likely to gain the public’s trust that institutions are acting in a legitimate and fair manner and that limit-setting is based upon values and principles (recall the unfavorable public responses surrounding allocation of penicillin during WWII and subsequently dialysis).

In formulating its recommendations, the TF considered the following overarching ideals, including, but not limited to, justice, fairness, maximizing benefit, and minimizing harms. The ultimate decision-making process employed by the TF is based upon a modified utilitarian model that maximizes total benefit, emphasizing lives saved or life-years saved.

On its own however, a strictly utilitarian allocation approach is insufficient. Although saving more lives inherently is preferred to saving fewer lives, perhaps the most obvious limitation to this practice is its lack of specificity. To account for such constraints, in its deliberations, the TF recommended prioritizing chemotherapy and supportive care agents between different diseases only when the scarce drug significantly contributes to survival difference as in the case of methotrexate for treatment of ALL compared to osteosarcoma. Within a given disease state, and perhaps even a subset of disease, the TF recommends that prioritization decisions should not be based upon factors such as patient age, size, or participation in a clinical trial. Select examples of specific considerations for allocation include:

- Allocation decisions should not to be based upon age, sex, development, socioeconomic status, immigration status, race, ethnicity
- Consider “curability” and/or prognosis, including the threshold of curability.
- Allocation decisions should be based on strength of data.
- Consider a drug’s importance or need to a given patient’s prognosis.
- Consider the critical role that certain drugs have in the management of cancers with poorer outcomes.
- Consider the total amount of the scarce drug required.
- Consider the phase of therapy.
- No prioritization for clinical trial participants.
- Patients and families affected by drug shortages must be engaged and appropriately apprised of decisions about their treatments.
Conclusion

Solving the drug shortage problem is an ethical obligation and a practical problem. While healthcare rationing is inevitable, rationing life-saving chemotherapeutics and supportive agents raises many ethical challenges. Physicians, and oncologists in particular, lack sound guidance in making ethically appropriate decisions for allocating scarce drugs.

In the absence of a much-needed national advisory statement on how best to allocate scarce drugs, and until policymakers and stakeholders can prevent future shortages, physicians must be able to make thoughtful and appropriate decisions when prioritizing life-saving drugs among equally deserving patients.

The proposed recommendations provide a transparent & defensible framework to assist providers and administrators. Furthermore, it provides reasoning for explicit decision-making in the face of an actual drug shortage and aims to minimize bias as might occur when individual clinicians or institutions are forced to make difficult, and at times tragic, rationing and prioritization decisions for children with cancer.

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The Author has disclosed no conflicts of interests.

Endnotes


Notes continued on page 45
Drug Shortages at Children’s National: An Interview with Dr Jeffrey Dome

Jeffrey Dome, MD, PhD, the Division Chief of Hematology and Oncology, sat down with Children’s National Pediatric Ethics Program to discuss the impact of drug shortages on the medical community. Specializing in chemotherapy, Dr. Dome has experience with the ethical issues that accompany old, generic, “injectable” drugs. Below is a lightly edited transcript of the verbal exchange.

Interview by Garrett Dome

Ethicscope: Hello Dr. Dome, thank you for meeting us at Pediatric Ethicscope. Hopefully this interview will be informative for both parties.

Dr. Dome: Thank you for taking the time.

Ethicscope: There are many facets of the drug shortage to be discussed. Seeing that you specialize in chemotherapy, I will keep the conversation more catered towards your expertise. However, I was wondering if you could tell me briefly about drug shortages at Children’s National. How does the hospital manage shortages?

Dr. Dome: The hospital has been very effective in managing drug shortages. Whenever
there is a shortage, the physicians and other medical staff inform the hospital; this way, we can always plan accordingly. Our model has prevented Children’s National from having any major deficiencies in drug supplies.

**Ethicscope:** Since most chemotherapeutics are administered by injection, oncology often suffers significantly more when a drug shortage occurs. In fact, chemotherapy is commonly ranked among the top five drug classes that are in short supply. At Children’s National, how does the Division of Oncology approach the shortage of sterile injectable drugs?

**Dr. Dome:** When shortages occur, there are several steps that we take to mitigate the problem. Firstly, we try and coordinate when chemotherapy is given. If two patients are being administered the same chemotherapeutic, often times they can share the same vial. Having the patients come in on the same day allows for sharing and prevents the hospital from letting excess go to waste.

**Ethicscope:** Do you think Children’s National does anything differently than other hospitals when preparing for shortages?

**Dr. Dome:** I am not sure; I will say that our pharmacy is proactive. Children’s National will reach out to other hospitals if necessary. In fact, the DC Metropolitan area has a network for sharing drugs; this way if a patient desperately needs chemotherapy a resource is always available. Another thing that we do, this being more of a last resort, is substitute certain drugs in a patient’s treatment regimen. Also, the Division of Oncology will alter the sequence of chemotherapy if necessary. For instance, a patient that is supposed to get drug x at a certain time may be given drug y at that time and then drug x later on.

**Ethicscope:** Would you say that sequence manipulation works with most patients or is it more on a case-by-case basis?

**Dr. Dome:** It is really on a case-by-case basis; for some of the treatment regimens, the order of the drug is more important.

“A recent survey of principal investigators (PI) and pharmacists at Children’s Oncology Group (COG) affiliated centers assessed the impact of chemotherapy shortages over a 2-year period on clinical trials (both COG and non-COG trials) and patient care. Fifty percent of COG PIs reported that at least one patient they cared for who was enrolled on a clinical trial was affected by the shortages and 66% reported that at least 1 patient’s clinical care was affected by the shortages. Equally troubling, 34% of pharmacists reported at least 1 near miss or actual medication error due to the shortages. Shortages of chemotherapy however, are not isolated to children. With over 1.6 million US adults diagnosed with cancer each year (compared to fewer than 15,000 children), older patients are especially at-risk.

Two surveys of medical oncologists assessed the impact of the chemotherapy shortages and lend insight to the severity of the problem. Nearly 83% of oncologists reported they were unable to prescribe their preferred chemotherapy agent; more than 75% had to make a major change in treatment such as choosing a different treatment regimen or substitute different drugs during treatment; over 40% were forced to delay the start of treatment; and 28% reported using a less-effective alternative because of a shortage.24,26 Perhaps most concerning was the fact that nearly 70% of oncologists reported that their hospital or practice lacked any type of formal guidance for how to make decisions about allocating drugs, prompting the authors of the study to appropriately call for formal guidance in this regard.”

“While we have so far been able to treat our patients in spite of the shortages, there is a likelihood that our patients will be affected in the future.”

–Jefferey Dome MD, Division Chief Hematology/Oncology, CNHS

**Ethicscope:** As a doctor at Children’s National, have you encountered a patient with clinical care affected by drug shortages?
**Dr. Dome:** I can think of a couple patients; fortunately with the system we have in place, shortages have not been a major problem. Of course, it is still a challenge for patients to get the drugs they need.

**Ethicscope:** It is good to hear that Children’s National is able to handle the issue.

**Dr. Dome:** We have been able to shield the patients well; it does require a lot of work and planning. But while we have so far been able to treat our patients in spite of the shortages, there is a likelihood that our patients will be affected in the future. Dr. Unguru has raised a serious ethical issue that requires ethically tuned decision making.

**Ethicscope:** In Dr. Unguru’s paper he talks about possible allocation methods for drugs in shortage. With the help of an allocation task force (TF), ranging in backgrounds from oncology to bioethics, an allocation framework was created. I have with me a copy of the framework; please look it over and share your thoughts.

**Dr. Dome:** I think the framework is a great start to address the problem. In step one of the framework, strategies to mitigate the shortages are introduced. These strategies are quite reasonable; some of them have already been implemented at Children’s National. It is nice to see a lot of approaches summarized in a single document. The tougher question is step two: despite the mitigation strategies a decision must be made. Physicians and parents are of course going to advocate for their own patient or child; there really needs to be an unbiased board capable of making these decisions objectively.

**Ethicscope:** Hopefully the allocation task force that Dr. Unguru proposes will be able to act as an unbiased bored capable of such decisions.

**Dr. Dome:** I believe we should prioritize drugs based on patient necessity and the likelihood of a significant benefit from treatment. Certain chemotherapy drugs have a questionable contribution to the overall cure of a patient; many hospitals use drugs based solely on history and tradition. Often times, there are alternative treatments that may lead to equally successful outcomes. For example, a drug that has been in short supply is methotrexate. In the United States, most osteosarcoma regimens will use methotrexate. However, some hospitals in other countries will use regimens that do not include methotrexate; yet they still have positive results. Perhaps methotrexate is not essential for the treatment of osteosarcoma.

**Ethicscope:** Although this does not mean the issues surrounding drug shortages are being solved; it makes us think about what drugs are a necessity. Do you have any other questions or comments on the framework?

**Dr. Dome:** Not at this time. Thank you for bringing this important topic to the attention of readers of Pediatric Ethicscope.
THE CASE:
Situation: A set of twins was transferred to NICU; 25-weekers who came in for a neurosurgery consult on Friday. They both had significant brain bleeds, white matter loss, and hydrocephalus. One of the infants was better off than the other, but both had midline shift and were seizing. The less well-off infant’s pupils were fixed and dilated, and he was septic.

Background: The parents are from South America, and have other children. The two parents were making decisions with no other support. This was a new relationship; they married recently, before the twins were born. The family had no prenatal care and no health insurance, but the mother stated she knew she was 25 weeks along.

Chronology of Events: On the first day, a family meeting was set up with a social worker, chaplain, PANDA team, and Spanish translator in attendance. Neurology was present to explain how poor the prognosis for the twins was. The family was counseled several times about transitioning from aggressive care to comfort-only care. It was explained to them that neurology was not going to consult because there was no therapeutic intervention they had to offer. Even after the prognosis was explained, the parents reported they wanted to continue, and would not put any limitations on care. Subsequently, head ultrasounds read by the head neurologist and radiologist determined the infants were 22-weekers, not 25-weekers; their brains were significantly underdeveloped.

Over the weekend, the team had more conversations with the family, focusing on the child who was worse off. The family agreed to not do chest compressions on that child after the team explained how “horribly painful” the procedure would be. However, the brain bleed and hydrocephalus became worse with the healthier child; his condition now more closely matched the sicker child. The children were clearly in pain. Due to the condition of their skin, it became very difficult to do lab work. Their heels were described by the nurses as “essentially gone,” which made it “horrible” for the team to provide care. Later that week, both children started to deteriorate. The parents got to hospital just in time for the sicker child to die in their arms. The other infant remained on the ventilator.

The parents appeared to be at peace; both babies had been baptized, which had been very important to them. As soon as baby passed away, many people showed up to lend support. It was frustrating to see all these people show up after the baby had died, rather than supporting these two young parents earlier in the process.

The other child continued to get worse for a week and a half. He extubated himself, and was not reintubated.

The condition of his skin worsened, and the team could no longer do lab work on him. Meanwhile, the parents became focused on little things: how much weight has he gained? How much has he grown?

The team continued to become more and more uncomfortable. The parents started coming less often, so the team backed off. A meeting was arranged to introduce them to the new attending physician. The remaining baby then died in parent’s arms. Family members and friends showed up again upon death. It was a very challenging 3-1/2 weeks.

All kids at CNMC are transferred, so there are many coming for a second opinion; many kids come in same predicament. It is very hard for everyone involved.

THE DIALOGUE:
Yoram Unguru: “Clinical ethics is about conflicting moral obligations. What do you think was the conflicting moral obligation here?”

Social Worker: “It was different for everyone. Many staff felt they were doing harm to kids. The nurses were the ones sticking needles into child every three hours. I can see the dilemma for the parents; what can be done to build trust with them? We know its bad situation from outset; on day one of admission, it was clear what needed to be done. There was not enough time to build a rapport. We worked to get parents to trust in a matter of moments. The team struggled with pain being caused.”

Physician: Parents are entitled to ask for everything, but are not entitled to have everything. There seems to have been lack of clarity among team. Looking at what other high quality NICU’s are doing, would anyone take these children? The scope of care for these kids is very limited. We end up providing futile
There is a lack of comfort with difficult situations with parents who are demanding everything.

**Social Worker:** The physicians were clear on what team was not going to do.

**Nurse 1:** We have to live with what we do, but parents have to live with it for much longer.

**Nurse 2:** “Doing everything” means something different to a family than it does to a clinician. It means parents can say, “I have no regrets that I didn’t do what I should do. It’s not about technology, or futility; it is about their being the best parents they can be in a situation everyone hopes never to be in.

**Yoram Unguru:** What was the basis for the transfer?

**Social Worker:** We didn’t have all the information; there was a communication gap. The family had gone to an ethics consult at the previous institution. The family relayed that they had been told there was some neurological intervention that could be done at CNHS, which turned out not to be true. At the time, images weren’t available, and the severity of the twin’s conditions wasn’t understood. The transfer team is not equipped to make such calls. They may presume the outcome will be poor, but it’s a very different matter to actually refuse transfer.

The original institution couldn’t make progress with parents, who believed CNHS had the resources to deal with situation. The thinking at the original institution was that the transfer would provide the parents with the feeling they had done everything.

**Audience Comment:** These babies are never going to leave hospital. Isn’t this a disservice to them? I understand we cannot withdraw care without the parents consent, and the physician had terrible feelings about the situation, but what is it like for those at the bedside 12 hours a day?

**Yoram Unguru:** We shouldn’t withdraw care without the parent’s agreement, but it’s unreasonable to put parents in such an untenable situation forcing them to make what for many parents, is a truly tragic choice.

We need to take the responsibility; we signed up for these types of situations, the parents didn’t. In part, this means reframing the options that are presented to the parents. Sometimes, instead of saying what we can do, we need to say what we’re going to do. This amounts to more than just withdrawing care, but presenting what can actually be done.

**Physician:** One problem is that different attending physicians have different decision-making frameworks; the parents were undoubtedly aware of that. There is a lack of consistency.

**Yoram Unguru:** What was the expectation of the parents at the time of the transfer?

**Social Worker:** We knew the situation, but we had to build rapport while putting limitations on what could be done.

**Yoram Unguru:** Was there a discussion of what would be done?

**Physician:** The family was expecting a neurosurgical intervention. The team explained neurosurgery wasn’t going to happen. The family didn’t want to be put into position of choosing to withdraw care. Most of the time, the family doesn’t have any medical education, or know how to make such a decision.

**Yoram Unguru:** No amount of framing the issue will bring parents up to speed. Parents focus on “the little things” because that’s what they can do and that’s okay - what else can they focus on? Often, based on our
experience with similar cases, we can play out what will happen, but the family's background, religion, etc, influence what ultimately happens and no two families experience illness in exactly the same way. We can't expect to establish rapport and get to know a family and their specific desires and needs in a short period of time when relationship building takes time.

**Nurse 1:** Why is it that we feel badly that we cannot convince family? Maybe this is the trajectory the family has to go through. Do we think we failed because we couldn't convince them-no. It feels badly that we cannot relieve what we feel is the pain and suffering of the infants.

**Nurse 2:** That feeling comes from feeling the parents were not part of the team in terms of agreeing with the course of care. Moral distress came from watching babies suffer. The team met every single day to discuss the case. Diaper changes were horrific.

**Ethicist 1:** There is an issue of trust. The family comes from South America. They may have had experiences with discrimination. Very often, there is a different meaning of ending care; a feeling of not being given something because of who they are. Overcoming this requires humility and cultural sensitivity. Perhaps a pediatrician who knows the family, or priest who can consult the family, could have been located. Had there been an ethics consult, those are some of the things we would have brought in. We often come to the conclusion that there is no reason to provide futile care. It reminds one of Dostoevsky: brothers who hate their father, for good reasons. Possibly one of them is so angry he may kill the father. Everyone tiptoes around the situation, and allow it happen. The parallel is that often the family is fighting an internal though that this cannot go on, but they cannot do it; through compassion, and perhaps friendship, this though should be supported. Often when you tell the parents what we are going to do, the parents will not object; rather, they will feel relieved. If they do object, that must be addressed, but no one is obligated to provide medical treatments that are not indicated.

**Yoram Unguru:** As doctors and nurses, we are trained to “fix;” coming to terms with not being able to do so is difficult. We have to be able to be honest with ourselves and those we care for. Parents deserve and respect that.

**Ethicist 2:** Coming from an adult-care clinical ethics perspective: In pediatrics, there is a very strong emphasis on getting parents to agree; a prima facie obligation to get them on board. That's defeasible; part of the justification for family-centered care is that parents have "good-enough" interest of child at heart, but they may not.

**Chaplain:** In the U.S. we have a very difficult problem discussing allocation of resources. We work hard to keep this out of the conversation.

**Yoram Unguru:** Dovetailing on my Leikin Lecture talk and the idea of allocation; prioritization or allocation is not the type of decision to be made at the bedside, rather, it's an important policy issue. Deliberative democracy is one approach to addressing allocation of scarce resources. It must involve people who have skin in the game; including the patients and families. In other countries, this case may not have gotten to this point because it's possible there would have been a policy-level decision to help guide things along and in doing so, possibly prevent some of the moral distress the parents and staff experienced. That's a very different situation, but worth keeping in mind.

**Audience Comment:** Is it justifiable to put these kids through three and a half weeks of agonizing pain to allow parents to come to terms with the situation?

**Chaplain:** Underpinning patient centered care is a partnership; terms we use such as "getting on board with" betray a different sentiment.
To work in pediatrics is to have hope. Every day in the world of pediatrics we hope that the work we do impacts the children we see for a lifetime. We hope they will grow, we hope they are strong. We hope the choices we help them make today lead to a path of health and happiness, and eventually to a fulfilling adult life. Suddenly, the end of that path becomes a bit hazy for the adolescent with chronic conditions; sometimes it is downright confusing.

Clinicians in the adult system are infrequently prepared to treat the variety of conditions seen in pediatrics, and the few providers who are available to this population struggle to absorb the growing number of older patients with childhood-onset disorders. Patients are frequently ill-prepared to take on the responsibilities required to manage their own care, and the pediatric system lacks cohesive, functional processes for teaching patients how to develop these skills. Our young adults with complex conditions often long to move forward, but they do not know where to go.

As medical care for the child with complex diseases becomes more advanced and sophisticated, so too grows the vacuum of care for the adult with childhood-onset conditions. It can be a great challenge for providers and families to bridge the gap from pediatric to adult specialty providers, particularly if the patient requires multiple specialties continue through the transition.

Many factors contribute to successful communication with adolescents about transition to adult care. Determining how the patient understands and values the process can guide clinicians’ efforts.

Bridging the Gap
The American Academy of Pediatrics has put forth a great effort in the past decade to support the concept of transitional care for the adolescent into adulthood through the primary care provider (2011). The Academy states, “optimal health is achieved when each person, at every age, receives medically and developmentally appropriate care.” There are transitional readiness assessment tools and algorithms to guide decision-making, but no customizable methods for the complex patient. There are recommended timelines for finding adult providers, but there is no assurance there will be enough willing practice groups. Our transitional care models remain largely conceptual, with high barriers to entry.
In the midst of these changes, young adults with high-need medical conditions can fall through the cracks and get into serious trouble. Without proper maintenance treatments and attention, this patient population goes by unnoticed until much larger problems surface. Additionally, many patients are independent enough to pursue the amount of care they desire without intervention from parents or legal guardians. As young adults continue to develop in maturity, they may not fully understand the long-term importance of structured follow up for chronic conditions. Adult spina bifida clinics reviewed in 2014 in Utah and Minnesota revealed that 85% of young adults seen for initial evaluation reported an active issue, 34% of which would require surgical intervention (Summers et al., 2014.) These outcomes are deeply disappointing for providers, costly to society, and often tragic for the patient.

Embracing the Process
The act of transitioning into adult practices is not a matter of a single event, but a product of dedicated work by many invested individuals. This process can be affected by many factors including how the patient understands and values the transition, and the number of transitions taking place at the time. For the cognitively intact patient, this transition may come around the end of adolescence, a time in life that is inherently stressful for young people. For the patient with psychosocial delays, a time for transition may be chosen around a disease-free interval (Lambert, 2015.)

Along with the change in providers, the patient may also have to consider changes to insurance coverage, informed consent, transportation and many other new adult responsibilities. It would be unfair and inappropriate to expect a young person to handle so many new issues alone. Providers, patients and their families share this responsibility, and need to develop a collaborative relationship. These efforts require a strong commitment from the patient and family, but the providers certainly take on a large part of the process. Providers frequently have clinics that are over capacity, and struggle to keep up with the needs of the populations they serve. At times, the adult transition of one patient may seem beyond the scope of the pediatric provider. However, the issue of transitional care has its basis in the very underpinnings of the medical profession’s ethical beliefs.

Breaking It Down
If the examination of ethics seems a bit esoteric, breaking it down to its four core principles helps ground it in reality: Autonomy, Justice, Nonmaleficence and Beneficence. Children becoming adults certainly brings to mind the concept of autonomy, as parents and providers learn to accept the choices of the developing youth. Much like parents, providers bear the responsibility of fostering a trusting relationship with their patients. From this relationship, patients gain the knowledge and confidence to serve them in their journey to adulthood, and beyond.

Youngsters need time to process these changes, so conversations about transitions are best had early and often. Practice makes perfect, as patients gradually take ownership of their medical conditions and learn to use the resources available to them. Finding an adult provider who is ready to accept a transitioning patient will take many resources, including knowledge of insurance coverage and existing local specialty practices. This may take a considerable amount of time; a point that should be communicated clearly to families and caregivers.

True autonomy can only exist when one understands all the rights and responsibilities allotted to an individual, and exercises them with purpose. Everyone
benefits from the creation of informed consumers. In the case of patients who cannot advocate for themselves, the care team supports the development of the legal guardianship necessary to promote the patient’s best interests.

Justice For All
In some cases, a decision of best interest can be made almost unanimously among a care team. When considering the best interests of society at large, risks and benefits are continuously weighed to maintain a careful balance. This system of Justice gives all citizens the freedom to pursue their goals with the knowledge that resources will be allotted fairly. Justice in healthcare is no different, and we expect no less. Fair distribution of goods and services results from accurate assessment of needs and priority of service delivery. The needs of individuals with chronic conditions are continuous and may increase over time, in contrast to the needs of an acutely sick child. Both levels of care are important, and failing either vulnerable population is a disservice to our system.

Justice is achieved in healthcare when patients are able to access and use the appropriate services at the right time. A study of adolescent and young adult Medicaid patients in North Carolina looked at the health care utilization rates in a sample of young persons with chronic conditions (Phillips et al., 2015.) The patients’ average age at time of diagnosis was 9 years old, and average age at the time of study was 19 years old. These patients with childhood onset conditions had significantly higher emergency department use, as well as longer inpatient stays during their Medicaid lifetime coverage. Although patients with chronic conditions are expected to have higher healthcare utilization, emergency department visits and hospitalizations are not the best use of resources.

Appropriate transitional care for the young adult with chronic diseases goes far beyond hospital doors. Educational level and professional success achieved into adulthood are tremendously impacted by the care established during transitional years. Standardized educational advocacy tools, such as Section 504 of the Individuals with Disabilities Act and Individualized Education Plans, are well known today. These tools help to promote schools, parents, and providers working together to ensure continuing education for special needs children. While far from a perfect system, these tools provide a framework for customized education goals. The process of moving into the workforce, if that is a possibility, can be even more challenging for an adult with special circumstances.

A longitudinal study found that approximately half of adults with childhood onset Systemic Lupus Erythematosus (SLE) were unable to achieve full employment after completing their desired level of education (Lawson et al., 2014.) In the American health care system, employer-based health insurance remains the dominant means of health care coverage. Persons with childhood onset conditions who do not have adequate support into adulthood may lose the ability to support themselves financially. Without proper insurance and access to long term follow up, inappropriate healthcare utilization increases. Justice is in jeopardy when patients with chronic diseases become a danger to themselves and a burden on society.

Start the Conversation
Providers practice nonmaleficence daily, considering the potential harm to a patient with every decision they make. Patients, however, did not take an oath to protect themselves; children and adults alike may frequently make questionable choices for a variety of reasons. A large part of developing independent young adults involves creating systems and boundaries. Parents and providers alike must allow children to gain increasing levels of freedom in preparation for adulthood. In the process of transition, the care team must foster an
environment where patients can develop a sense of Nonmaleficence to apply towards their own care.

Caregivers feel a heightened sense of responsibility over medically complex children, often sheltering kids from the realities and responsibilities that their management entails. To ensure their safety as they grow older, patients must gradually gain an understanding of the risks associated with their chronic conditions. Children want to be engaged by their providers, become knowledgeable of their conditions, and take on challenges. They only need the tools.

Setting patients up for a successful transition requires starting the conversation. The concepts of beneficence and nonmaleficence prescribe balancing the good we do for our patients with the potential harm that doing so may entail. Transitional care is an example of an action whose benefits far outweigh any potential harms. In fact, if the transition plan is properly executed, there will be no harms in the sense in which nonmaleficence is generally understood; the burden of learning to manage one’s medical care is one which cannot be avoided. Moreover, learning the skills necessary to do so is of benefit to the patient in that those skills can be used in other aspects of life where decisions must be made in light of evaluating one’s circumstance. Taking action towards the good of the patient encapsulates Beneficence, and allows the care team to move beyond the conceptual model of transitional care, the healthcare team. There are many models to help begin the planning for the transition from pediatric to adult provider. Each patient will need a unique plan that works for everyone the care team involved. There can be timelines, goal sheets, check lists and coordinators; but above all, there must be a commitment. Patients and parents, or caregivers, must make time to incorporate changes and planning. Providers must keep the dialogue going, and offer support where needed.

With time, patience and strong communication, the role of transitional care in the community will expand. Medicine always adapts to the needs of the population, and these needs will only continue to grow. Patients and providers must advocate for health care changes that support the current landscape. Increasing the number of adult providers with experience and training in childhood onset conditions will be crucial to the safety of complex transitions. Care coordinators and case managers dedicated to this cause are invaluable to patients and families. As processes improve, there may be gaps in resources that are unforeseeable at this time. So long as there are dedicated individuals who care about making significant changes, there will be hope. To work in pediatrics is indeed to have hope, and we are here to keep that hope alive.

“Unless someone like you cares a whole awful lot, nothing is going to get better. It’s not” – Dr. Seuss

References


In recent years, dealing with drug shortages has become an integral part of a pharmacist’s work [1]. Drug shortages can range from basic parental electrolytes and antibiotics to life-saving chemotherapy. Unfortunately, dealing with chemotherapy drug shortages is more of a challenge; often times there is no alternative therapy for the patient, making the ability to procure the drug equivalent to the ability to treat the patient. In the past, it was not unusual for the pharmacy to be turned into a call center at such times [2]. While it is still time-consuming, it is no longer necessary to call fifteen pharmacies to find a medication in short supply; we have developed systems to manage shortages that increase reliability, efficiency, and safety [1]. Nowadays, dealing with drug shortages is part of daily practice and, most institutions have weekly meetings devoted to drug shortages.

Procuring Drugs for Patients
On a regular basis, pharmacists check online lists for all current drug shortages, which are distributed and maintained by ASHP. Hospitals generally obtain the drugs they need from wholesalers, of which three companies dominate the market, Cardinal Health, McKesson Corp., and AmerisourceBergen, which account for 85% to 90% of the distributor market [3]. We check with our wholesalers inventory weekly, and of course, our in-house stock daily. Reconciling
these inventories allows us to plan for our patient’s pharmacotherapy needs. The process involves determining from providers what course of treatment each patient needs, and at what time, and ensuring we will have the product available when needed. Once all this information is known, we sequester the medication for each specific patient.

Sequestering ensures that for each specific patient, the necessary doses for the course of treatment will be available. For Erwinia, for example, that means 6 doses; it is better not to give it at all than to only give, say 4 doses, so the medication for the entire treatment course must be assured ahead of the start of therapy. This means that the total in-house inventory of a drug at any given time is not necessarily indicative of what is available to treat newly diagnosed patients; much of the product may be sequestered for existing patients.

In addition to what is sequestered, we run usage reports to determine how much of each given drug we need to keep on the shelves (‘PAR’) to manage the influx of newly diagnosed patients. The PAR is based on our past usage of each product, and reputable wholesalers track the purchase history of each given hospital. Information about upcoming shortages might prompt purchasers to “stock up,” so the purchaser’s purchase history is used by reputable wholesalers to limit future purchases. If an order is much larger, we have to explain why we need the additional products. Many times, we have to email the drug company directly with new patient starts, to ensure drug delivery. However, not all wholesalers use such a process, making it possible for unscrupulous buyers to stock up when shortages are expected.

Despite this system, shortages persist, causing frustration, worry, and sometimes, outright fear—among patients and health care providers alike. The reconciliation of what our wholesalers have in stock, what we have on the shelves, and what manufacturers report they will be supplying appears deceptively quantifiable; with those quantities known, it would seem possible to determine precisely what a hospital will have available for patients at any given time. However, in practice it is not so simple.

To understand why this is so, it is necessary to look more closely at the supply chain from manufacturer to end-user, a process that introduces its own potential liabilities. It is these elements that can contribute to, or exacerbate shortages, and thus are ethically noteworthy in any discussion about the ethics of drug shortages and their management.

If a particular drug is not available from our wholesaler, our procedure is to go directly to manufacturer and call their medical science representative or drug sales representative. We work to maintain good relationships with manufacturers for just this eventuality. However, if a manufacturer says, “we will be delivering x product on February 1st,” a number of other factors must be considered to ensure our providers can administer the drug they need when the patients need it. For example, as of this writing, Erwinia is currently in short supply, and while we have a lot of contact with the drug representative, and spoke daily with medical science liaison when the shortage was announced, it is produced by only one manufacturer whose manufacturing facilities are abroad. Erwinia has to go through a vetting process and clearance through customs, a process that can take weeks.

So, we can be told a drug will be available on February 1st by the manufacturer, but we may not be able to actually take possession of the product until March 1st. Even estimated arrival dates based on the vetting and customs processes are not hard and firm; February 1st can turn into February 14th; that can result in the delay of a treatment cycle that can have clinical effects on our patients.

Sometimes we have to have two different concentrations of the same medication. For Cytaribine, the national standard is 20 mg/ml, but everyone needs it; so now we can only get 100 mg/ml. Errors can be introduced into the process when different concentrations must be converted, or an alternate may have a similar name, but require different dosing. In such situations, we send out multiple emails and retrain staff. However, when trying to get whatever is available, iatrogenesis can occur; harm may be caused to the patient by the medical treatment intended to help them. In this setting, there can be transcription errors or dosing errors, arising from working with different concentrations, or failing to follow alternative preparations that may be required [4].

Financial Factors
Unfortunately, money is made from drugs that treat breast, colon, and kidney cancer; the quantities of medication needed to treat children with cancer are...
only a small percentage of those [5]. As a result, the focus on pediatric cancer needs is less than those of us working in pediatrics would like. If a drug is dual use, i.e., it can be used to treat adults as well as kids, there is less likely to be a shortage, but for a drug like Cytarabine, for example, for which there is no alternative, a shortage presents a scary proposition because the incentive to produce it in the first place is marginalized by higher-profit products.

That is not to say there is no money to be made in such medications. The wholesale system in the United States has been described as the “weak link,” in the drug distribution chain [6], but within that framework the shortages of drugs have created a pocket industry of speculators, the so-called “gray market.” The gray market is comprised of “alternative wholesalers” who track drug usage and production so as to determine what will be in short supply [7].

Not all alternative wholesalers are bad actors, and in fact, hospitals need alternative wholesalers who maintain the pedigree of their products. The pedigree of a drug confirms it has never left the custody of reputable wholesalers who operate within the mandate of the industry’s best practices. Wholesalers may join the National Association of Boards of Pharmacy (NABP), which investigates members’ operations; the organization goes out to their facilities, performs inspections, and ensures their drugs have never gone outside the wholesale chain. Visual inspection is necessary, as the NABP reports:

“Even with pedigree requirements in place, suspect wholesale distributors have found ways around the system by falsifying their drug pedigrees.” [8]

The supply chain can be thought of as akin to evidence collected by the police; there is a chain of custody, with each step accounted for. This ensures the drugs sent from the manufacturer stay within the wholesale chain, at least in theory; there are bad actors in the gray market, purchasing drugs to resell at higher prices, and the distinction between primary and secondary wholesalers is not always clear cut; sometimes primary wholesalers end up buying products from secondary wholesalers [9].

Drug production is a long process; it is often projected six months or more in advance by manufacturers [10]. Knowing this presents opportunity in the minds of bad actors; when a shortage occurs, even if the manufacturer responds quickly, it will be months before more product is available. In the meantime, many patients can’t possible wait 6 months, or more, to be treated, and will turn to the gray market.

As discussed in What Lies Beneath (in this issue) demand for medicine is inelastic to price; unlike a watch, a new car, or other consumer purchase, if a patient needs a medication, they simply need it, and in most situations will not turn away because of cost. In pediatrics, this is especially so; parents will pay whatever they have to in order to ensure their children are cared for.

Abuses
The process of the bad actors works as follows. The wholesalers make speculative purchases based on their research, buying up product that they anticipate will have more demand that supply. When we do obtain drugs from the gray market, it is always at a significant price increase [7]. Some sources cite price increases of several thousand percent [11,12]. This is the reason that reputable wholesalers use a purchaser’s traditional purchasing history to limit purchases, and the reason that the ASHP site administrators don’t even announce a shortage that is less than 30 days old; doing so would provide the gray market bad actors with the information they seek.

Some gray market players are knowingly buying up drugs they shouldn’t have been. A home infusion company could buy from a Cardinal, walk across their loading dock to their “sister” company, and resell the drug. However, that resold drug would not have the pedigree we require at Children’s National; we do not buy from sources that don’t have a record of responsible transactions, and if the drug ended up here, we would send it back. However, in situations where life-saving medications are in short supply, the market is fertile for abuse; as demand increases, or is not met, people become desperate. What could cause more desperation than not being able to obtain a life-saving drug for one’s child? Even counterfeit drugs have become a significant problem, particularly for those who cannot afford the pedigreed versions [13].

Speculating pulls excess out of the supply, through wholesalers who do not use a “dynamic allocation” process to check users purchase history [14]. This is where we see what we refer to as “leakage.” Even if it is only a 5-10% leak out into the gray market, that’s 5-10% we don’t have access to at less than ransom prices. If viewed in utilitarian terms of costs and benefits, weighing the benefit to the wholesaler bad actor versus the cost to the child who needs Erwinia, how could that calculation possibly not come out in the child’s favor? The enrichment of an individual or group...
cannot weigh more heavily than the life of another. Even if one argues that the individual or group uses the money they make on such transactions to care for their own families, there are alternatives to engaging in drug shortage speculation; there aren’t alternatives for the children, or adults, who are harmed by not having access to these drugs.

However, a more powerful argument can be found in a principled assessment of this behavior. These bad actors are gaming the system to the detriment of all; as we have shown, there are other, significant hurdles for pharmacy to tackle to obtain the drugs that physicians and patients rely on, and the parasitic drag introduced by speculators creates uncertainty in a system which society must be able to rely on as a whole, and which any individual may come to rely on through chance or accident. It is therefore in both the individual’s and the public interest to close the loopholes currently being exploited.

The Drug Supply Chain Security Act, also known as ‘Track and Trace’ is a law passed as part of the Drug Quality and Security Act in 2013. Over time it puts in place mandates for manufacturers to have sequential lot numbers that can be used to track drugs to end users at all points in the supply chain. The law goes into full effect in 2020, and may help resolve some of these issues. However, a manufacturer who finds they’ve only sold 50 of some product is not going to suddenly make excess which they know will not sell. It doesn’t make good business sense to do so. Yet, this is what needs to happen from a healthcare point of view; we need the excess to ensure we have enough of these drugs to treat each patient diagnosed. The alternative to having excess, unsold drug is having untreated patients for whom no drug is available. Closing the speculative loopholes is a step in the right direction, but the fundamental issues of commerce versus compassion remains unresolved.

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Endnotes
Overview
Everyone wants sick patients to have access to the medications that can help them; divisions form between two groups, roughly according to the specific principle, or principles, each group deems paramount. The issue of drug shortages can be framed as those who wish to ensure drug availability in virtue of dedication to the patients’ interests, on one hand, and those who herald economic responsibilities, on the other. The former group maintains this is an ethical issue; the later contends the economic realities cannot be ignored. In situations where one group insists an issue is “ethical” but the other disagrees, an impasse is formed; if two parties cannot agree on the premises of an issue, no argument is even possible. To wit, in a 2013 article titled, “Why drug shortages are an ethical issue”, authors Lipworth and Kerridge outline the causes of drug shortages, but conclude:

“It is an open question whether these behaviors represent unethical conduct or are simply “rational” behavior in a market system.” [1]

In Philosophy, the study of ethics is a subset of the study of value in general. Whereas ethical values are often characterized in terms of “right” or “wrong,” the characterization of one’s work, interests, and politics are often expressed as “good” or “bad.” These examples are not ethical values, but values of this more general type [2]. The study of this type of value is classified in philosophy as value theory, or Axiology. Axiology includes the study of ethics, the study of aesthetics,
The Conflicting Principles Underlying the Drug Shortage Crisis

and this general type of value as its subject matter. All ethical problems are in that sense axiological problems, but the reverse is not true. In considering the issue of drug shortages, or drug pricing, sometimes we may think we are speaking a different language than pharmaceutical industry representatives, and the pharmaceutical industry likely feels that way when talking with the FDA; in an axiological sense, we are speaking different languages. The purpose of this article is to expand from ethical analysis to include, pari passu, values in this larger sense. An axiological examination can provide an overview of both ethical and other values, a lingua franca, of sorts, from which to fruitfully draw conclusions about the issue of drug shortages as a societal ill.

But it may be that different sets of values are incommensurable; there may not exist a way to develop criteria that can be used to critically assess these varying values. In aesthetics, most would probably agree that we can’t compare what one person appreciates in a painting with different things another appreciates, and say one is a “better” way to appreciate the art. A fair enough criticism, but if two different value systems share common elements, we can take the values common to both, such as, for example, being consistent, telling the truth, or obeying the law, and examine the conflict in light of those shared criteria. The result would be, if not indicative of a definitive course of action, indicative of improvements to be made. In the most general sense, drug shortages are caused, ultimately, by our societal values; the choices we make about how we want our health care delivered, the power we vest in our government, and the economic system we endorse. One commentator noted, “Our value-laden social, political and economic choices are obviously contributing to drug shortages.”

This article proceeds as follows. First, an overview of the history of drug shortages and their effects will set up the values in conflict. That is followed by teasing out the reason drug shortages are inherently linked to drug prices. That leads into the question of motivations, the “why” and “how” of pharmaceutical industry decision-making, which will be explored with an eye to historical context. With that in hand, two examples will be considered, both of which will be shown to be proxies for industry behavior and social expectations writ large. All the parts will then be in place to examine some general values common to both value systems, from which conclusions valid from both perspectives may be drawn.

Drug Shortages History and Breadth

Drug shortages began escalating in 2005. By 2007, the FDA listed 154 drugs in short supply; that number reached an apex of 456 by 2012. At the beginning of 2016, more than 300 drugs were in short supply. Because some drug shortages persist for multiple years, the total number of drugs in short supply continues to escalate, as shown in Figure 1. This finding is born out in practice as shown by the research of Metzger et al., as cited by Yoram Unguru in this issue of Pediatric Ethicscope, and by a 2016 survey conducted by the American Academy of Pediatrics (AAP). The AAP study found that over 72% of the study’s 365
respondents, representing both general pediatrics and seventeen distinct pediatric subspecialties, experienced increased drug shortages over the past two years [10]. These shortages can leave even the most prepared hospitals unequipped to treat their patients should such a need arise. This and other problems resulting from drug shortages have been highlighted by Dr. Unguru, his colleagues, and numerous other physicians who have encountered this problem and are working on behalf of their patients to resolve it [11-13]. But even a cursory look at the titles of any of the numerous news stories that have been written over the years to alert the public about drug shortages reveals startling charges of unethical conduct at one extreme, and capitalist resoluteness at the other [9,14-16]. Research and academic works fare better, but it would be inaccurate to say the issue is not polarized [17].

The overall costs to society of shortages are difficult to quantify; the values involved include time, money, professionalism, and health, to name a few. Hospital pharmacists must spend time searching for drugs (described by Dr. Jeffery Dome in this issue), physicians must spend time developing and implementing alternative treatment plans, patient stays can be longer, or involve more other hospital services as less effective therapies are employed, with potentially inferior outcomes. Patients, physicians, and hospitals experience delays in many drugs that are not considered or reported as shortages. A 2011 study done by the healthcare provider alliance Premier, found that more than 400 generic drugs were backordered 5 or more days in 2010 [18] requiring staff to attempt to effect procurement at least twice in each instance.

Their other findings are staggering:

- 89% experienced a drug shortage that may have affected patient care, and that occurred more than six times for over half of those.

- 80% experienced a drug shortage that resulted in a delay or cancellation of a therapy or intervention, and that occurred more than six times for 30% of them.

A study by McLaughlin et al., found 40% of the 193 pharmacy directors who participated reported between one and five adverse events “probably or possibly,” associated with drug shortages at their institution [19].

All these issues result in manifold increases in the cost of medical care. According to a 2013-2014 study done by Premier, searching for alternative treatments costs hospitals at least $230 million more per year than they would otherwise spend in the wake of the drug shortage epidemic [20], down from $415 million in 2010 [21]. The financial cost of the drugs themselves is staggering [22], growing several points in excess of the growth of healthcare expenditures overall [23]. If a brand drug must be substituted for a generic many times the typical cost will be incurred; if brand drugs aren’t available, resorting to the gray market to obtain a lifesaving therapy can visit as much as a 4,500% markup (650% average) upon the patient, hospital, and health system [21]. The human costs are no less staggering; numerous deaths have been linked to the effects of shortages according to recent reporting [15,16].

While one may assess such findings in generalized terms, which is appropriate to policymaking, these statistics are comprised of many thousands, or millions, of individual cases, cases in which physicians’ efforts to treat their patients may be effectively stymied by an inability to employ what is often their best, or only, resource: pharmaceuticals. And the human costs? Leukemia & Lymphoma Society’s Vice-President for Research Communication, Deborah Banker, speaking to the Washington Post in 2011, put it succinctly. Referring to the effects of the then-current cytarabine shortage:

“With this drug they can be cured and without this drug too many of them will certainly die. That’s the simplest way to put it. The disease progresses so rapidly that untreated patients can sadly die within days. There is no time for delay and no certainty of a good outcome if you can’t get a full dose.” [16]
It is therefore a natural question to ask, “Why is this happening? What processes are at work such that this is the result, and what are the values at work?” In the charts put out by the GAO and FDA (See Figure 2, page 33), the categories listed as causes of drug shortages are: Supply/demand, Manufacturing, Regulatory, Discontinued, and Unknown [26]. At 57%, “Unknown” is the largest category, and while numerous reports indicate business decisions are perhaps the leading cause of shortages [25,7], that most salient fact is difficult to locate at all in official reports put out by the governmental bodies charged with oversight of the pharmaceutical industry” [26,27]-perhaps because attribution to human decisions invites value-based judgments.

In response, it has been argued the pharmaceutical industry is a large, labyrinthine even, enterprise that defies generalization, subject to demands of continuous innovation, and incorporates high risks [25,37-52]. But those facts alone do not foreclose all efforts to understand the dynamics of the problem. There is information from which at least preliminary conclusions may be drawn [25], insights that perhaps can eventually serve not only the patient populations affected, but also the public interest at large. However, a purely ethical framework seems to lead to a polarization of positions, with neither side willing to acknowledge the legitimacy of the values held by the other [28]. One central argument that will emerge is an empirical finding: the issue of drug shortages is inexorably tied up with the problem of drug pricing, for as it will be shown, the later induces the former. Underlying this dynamic is a conflict of ends; physicians uphold a fiduciary duty to their patients, whereas the pharmaceutical industry’s fiduciary responsibility is to its stockholders [b] [29].

The Industry Develops: Roots, Innovation and Blockbusters

Yoram Unguru points out recent reporting on the “availability of generic drugs, and chemotherapeutics in particular, is directly linked to decisions by manufacturers that either delay or prevent these drugs from becoming accessible” [11]. Many contend such tactics have a financial basis, a sentiment the industry challenges. Complicating matters, drug companies do not make their internal decision-making processes available; Angell quotes New York Times reporter Robert Pear, who in 2001 contended, “The basic problem is that all pharmaceutical costs, including research, are in a black box, hidden from view. There is no transparency.” [30] While the actual costs of drug development are unavailable for public scrutiny, the public is invited to presume such costs are extraordinary, thus justifying drug pricing [25,31]. However, no consensus of faith exists, nor, despite being an empirical matter, does governing corporate law require any divulgence of facts. As a result, an impasse exists; contentions of fact, lacking an undergirding trust, are assumed to be false. Yet, one can surmise what is going on inside “black box” and make deductions from macro-scale industry behavior, economic outcomes, and the resulting industry trends; one can look at accepted business practices and applicable laws. One can also use the tools of ethical analysis, from the perspective of industry.

In narrative ethics, the patient’s story is considered as a means to understand her values and interests, thereby allowing for a more nuanced understanding of the case, informed by the motivations, the stories behind those motivations [32]. What follows is application of that process to the pharmaceutical industry, to explore the values and interests concomitant with drug shortages; again not as an ethical critique per se, but as an axiological analysis.

A historical perspective aids this inquiry. In the mid to late 1800’s, drug companies such as Merck and Eli Lilly were what are commonly now referred to as “snake oil salesmen,” selling products containing quinine, morphine, cocaine, and heroin [33]. But like the regulations governing biomedical research, which have aptly been described as having been “born in scandal,” [34] it took the deaths of thousands of people, and countless infants who were unknowingly given opiates, for Congress to act; the 1906 Food and Drug Act required listing ingredients of medications on product labels, and was the first step towards today’s regulatory schema [35]. The Food, Drugs, and Cosmetics Act of 1938 required toxicity testing, establishing the beginning of double blind studies, much to the drug industry’s chagrin [36]. The introduction of Penicillin marked the turning point in the industry’s public image, as Syphilis rates in New York City were cut by 75% between 1943 and 1953 [36]. The intervening of World War II, and penicillin’s role in life-saving had a

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a. Even the Pediatric Oncology Working Group Consensus Statement (DeCamp et al. Pediatrics. 2014;133; e716-e724.) makes only indirect reference to the values conflict: See Recommendation 1, Background: “Working with the Department of Justice to... report exorbitant pricing” (at e718); Recommendation 6, Action Item 1: “emphasizing transparency as a value in planning processes, including financial analyses” (at e722).

b. I use the term “duty” to refer to physician’s fiduciary obligations to denote its ethical nature, and “responsibility” to denote Big Pharma’s obligations to denote it is in some sense different. The power dynamics of the physician-patient relationship requires a level of trust, and generally, a lack of understanding of the decision-making process not paralleled by financial investors.
profound effect; Paul Starr notes, “During World War II, the research effort that produced radar, the atom bomb, and penicillin persuaded even the skeptical that support of science was vital to national security.” [37] Whereas between 1900 and 1940, the primary sources of medical and pharmaceutical research were private, with groups like the National Academy of Sciences opposing any large-scale Federal funding [3733639], the NIH’s budget, $180,000 in 1945, swelled to $874 million in 1970 [36].

The importance of the American system of medical care delivery had a profound effect on our conceptions of the ethics of drug shortages. During the ascent of modern medicine, a page of Time magazine was devoted each week to modern advances and “wonder drugs.” This was evidence life was getting better [37336], as Henry R. Luce of Fortune magazine called it “the American century,” and Fortune’s editors referred to capitalism’s “permanent revolution”[37336].

However, the purchase of drugs was uncoupled from the consumer relying on them in two ways: only physicians could access the most potent ones, and insurance companies were handed the bills [38]. According to Philip Hilts, author of Protecting America’s Health: The FDA, Business, and One Hundred Years of Regulation, pharmaceutical industry profits reached 19% after taxes in 1957, and “were unlike anything seen in the history of sales.” [38] At the same time, the decoupling of payment from consumer, and growing success in the industry, left, “all concerned consuming the novel meds—the new American birthright—in ever increasing quantities.” [363937338]

So, while penicillin recast the industry as purveyors of social goods [36], drug companies are, and always have been, in the business of making money, like any other company. Unlike physicians who see their principal duty is to their patient’s best interests, Big Pharma sees its responsibility is to its stockholders, who could invest their money elsewhere. While physicians developed a profession centered on principles society endorsed, Big Pharma contended with what some see as an arrogation—an obligation to patients in virtue of the product they produce.

The growing power of the industry, represented by the tremendous growth of the NIH in the postwar years, had both formative and definitive effects on both behavior and policy. Marcia Angell, former New England Journal of Medicine editor, points out in The Truth about Drug Companies, that between 1960 and 1980, prescription drug prices remained a relatively static percentage of GDP, but from 1980 to 2000, that percentage tripled [255]. What accounts for the remarkable 9.9% annual growth in drug spending for that period? According to Angell, Reagan Administration policies “Let the good times roll” [256] through legislative efforts aimed at “technology transfer”, the transfer of basic research into marketable products.

The story of one such effort begins with Senator Birch Bayh (D-Indiana) and Robert Doyle (R-Kansas), who sponsored the Birch-Doyle Act [39]. The Birch-Doyle Act enabled businesses and universities to patent discoveries funded with public research dollars, such as NIH-funded research, and then to grant

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C. “Best Interests” here is being used in a general sense. This is not to say best interests is the sole criteria a physician acts on.
exclusive licenses to drug companies. As a result, drug companies no longer needed to rely on their own research. Even if they had, the opportunity to access the work being done at universities across the country would have been irrational to pass up. A comparison of the two accompanying maps of the United States illustrates the results (Figure 3, page 35.) On the left is a map showing the allocation of government funding to research universities. On the right is a map showing the locations and concentrations of biotech and pharmaceutical companies. Birch-Doyle had a significant impact on the creation of the Biotech sector of the U.S. economy (although the trend was already underway prior to 1980) by promoting the transfer of basic research into practical products.

It is apparent from both the data and the geographic locations of these companies that federal funding is a principal, if not primary, source of the research that industry draws from in the development of drug products, but that is not necessarily problematic; their products could still broadly serve patients needs. And while one can understand the desire to mitigate the risks of spending money on basic research, there is a point at which risk aversion has a deleterious effect on advances in patient care. This point represents a conflict between the industry’s valuation of its own business security and the patient's/physician's/hospital’s (and perhaps the public’s) valuation of the patient affected as a social ill.

However, empirical evidence suggests that risk aversion in the pharmaceutical industry is significantly greater than Pharma marketing purports. Angell points out that “me too” drugs comprise a significant proportion of the drugs being produced. In the period from 1998 to 2002, of the 415 drugs approved by the FDA, only 14% were innovations. 9% were old drugs modified in such a way as to be patentable as “new,” leaving 77% that were, according to the FDA, no better than existing drugs on the market. In 2013, of the $300 billion in sales reported by the 13 Big Pharma companies, $123 billion no longer had patent protection, meaning the pharmaceutical industry sold more generics than the generic industry itself, which returned $70 billion that year, and that was an 18-year high for the industry. Angell argues this occurs because of a “crucial defect” in the law; new drugs do not need to show they are superior to existing drugs, only that they are effective compared to placebo.

The central claim those who advocate “comparative effectiveness” approaches to drug studies is this: shouldn’t studies be done comparing the newly proposed drug to those it is intended to supplant? In practice this is not often done, and the reason cited is that showing any difference would be difficult without resorting to large (and therefore expensive) studies; it is difficult enough to show effectiveness compared to a placebo. According to Robert Temple, MD, Deputy Center Director for Clinical Science at the FDA:

The main difficulty with doing comparative studies is that the effects of most drugs, while valuable, are not very large, so that even showing a difference between the drug and no treatment (a placebo treatment) is not easy.

It could be argued that even 14% is significant for the patients whose conditions are ameliorated by the

“After years of defending high prices as necessary to cover the cost of research and production, industry executives increasingly point to the intrinsic value of their medicines as justification for prices.”

– Alex Berenson
Respectable opinion did not favor "commercialism" in medicine.

—Paul Starr (1982)

The molecule used in Gleevec was based on the "Philadelphia chromosome," so named for the University of Pennsylvania, where researchers Peter Nowell and David Hungerford discovered it in 1960. [43] The Philadelphia chromosome carries a gene involved in the production of bcr-abl tyrosine kinase, an enzyme that causes white blood cells to become cancerous because the kinase remains permanently active, driving cell division. In 1988 an industry researcher at Ciba-Geigy, Nick Lydon, approached Brian Druker, a researcher at Oregon Health and Sciences University, about developing a drug to block particular enzymes thought to be causal elements in some cancers. Druker suggested CML, and investigated a number of compounds Lydon had developed based on the Philadelphia chromosome [256].

Druker found one, STI571, which inhibited the CML cell action; in fact, it killed all of the CML cells in petri dish. Ciba-Geigy patented the compound in 1993, and by 1995, STI571 was ready for clinical development. In 1996, a merger occurred creating, Novartis and bringing a stop to development of STI571. Lydon left the company, but Druker pressed the new management to continue the work. They resisted [44]. Druker, Lydon, and Memorial Sloan-Kettering Cancer Center researcher Charles Sawyers had found imatinib mesylate successfully suppressed the growth of cancer cells while not affecting healthy cells, a highly unusual finding in cancer research, where chemotherapeutics generally work by targeting cell division in general [45,46]. With Novartis management not interested, Druker persisted. With limited support, he was able to begin Phase 1 trials. He demonstrated incredible results in 1999; once patients were given effective doses, Druker got a 100% response rate to the drug [44]. Angell argues, "Most of Novartis's R&D investment in Gleevec was made years after there was good scientific evidence to suggest that the drug would be useful." [256]

That may be true, but Novartis would have undoubtedly developed the drug if they knew what would result. Given that 9 out of 10 drugs that reach clinical trials don't make it to market [47], and by definition those ten have “good scientific evidence” supporting their development, the chance was only one in ten that imatinib mesylate would be a “hit.” Rather than being a function of rationality or risk, the difference in what Angell would presumably have done, and what Novartis did, was likely one of value; a physician and former editor of NEJM has a different relation to the imatinib mesylate findings than a business insider or economist. We know this intuitively, and take it into account when speaking with people, expecting people of different backgrounds, who have made different choices in their lives, to have different opinions on matters of value, and thus different assessments of risk. It is clear this is an axiological difference, but it is not clear it is an ethical one. Even the very rich could quickly go broke trying to fund ten out of ten compounds with “good scientific evidence” of potential benefit.

Looking to the more recent past, after adjustments for inflation, spending tripled again on prescription drugs between 1997 and 2007 [48]. During those two decades, “blockbuster” drugs, those selling in excess of $1 billion in the United States, increased from six in 1997 to 52 in 2006. As a proportion of all sales, that represents an increase from 12% to nearly 50% of all drug sales [48]. But in order for sales of “blockbuster” drugs to increase, one of two things needed to happen. One, drug companies could add production capacity, or two; they could reallocate the production capacity they already possess.

In either event, production of less profitable drugs decreases. In the former case, decreases occur as a percentage of total drugs being produced; in the latter, decreases occur relative to what was produced previously. Businesses exist to make a profit, and a CEO who did not reallocate resources so as to produce the greatest return for her stockholders would not be meeting her fiduciary obligation to them [29]. This basic economic reality is the missing component in the “Causes of Drug Shortages” charts. To be fair, some charts by other organizations include “business decision” as a category, but generally list its contribution to be less than 10%. As investment banker Lawrence Perkins stated in a Western Journal of Medicine commentary, it should not be any surprise...
that drug company decisions are based purely on making money:

“Regardless of what a company is selling, they are in the business of making money and satisfying their fiduciary duties...Chandrasoma argues that pharmaceutical companies have an obligation to society to produce medicines that address all afflictions and to avoid discriminating against a particular disease or condition. But pharmaceutical companies have to discriminate because, like other commercial enterprises, every day they must answer the following question: can we afford this venture? This decision must be based purely on sales and costs.” [29]

“can we afford this venture?” is disingenuous. We are not talking about financial solvency; as Angell points out, the pharmaceutical industry is tremendously profitable. In 2015-16, Pharma, Biotech and Life Sciences returned consistent net margins of between 19.5% and 20% [49], tied with the highest performer, banking. The pharmaceutical industry has been returning profit margins well above most other economic sectors for many years [2574-75]. By way of comparison, oil and gas companies, and automakers, returned profits in the single digits [50]. The extent of Big Pharma profits cannot be overestimated; in 2013, Pfizer’s profit margin was 42% [51].

Whether it was the shortage of childhood vaccines in 2000 that followed the 1994 CDC market cap on inflated prices, or the chemotherapeutic shortages discussed in this issue of Pediatric Ethicsscope, the underlying issue is the competing fiduciary duties at work. As Mark Goldberger, who coordinated the FDA’s response to the vaccine shortage in 2001, stated:

“We have to give approval for companies to make the drugs, but companies can leave the marketplace anytime they wish.” [52]

That being said, there are value-based concerns within the set of values industry accepts: capitalism. Selling anything and everything, regardless of its impact on the people who use it, is considered neither good business, nor legal. The 1906 Food and Drug Act requiring labels, the 1938 Food, Drugs, and Cosmetics Act requiring toxicity testing, and a range of modern laws have improved the industry’s ability to remain competitive and acceptable in modern society. Being truthful about one’s products is also a capitalist value, and importantly, competition is a capitalist value. However, there are industry actions that do not appear to meet either values expected by capitalist society at-large, or the more demanding expectations of ethical conduct.

The Case of Mechlorethamine
Mechlorethamine is perhaps the clearest example of a lifesaving medication, a stalwart of pediatric cancer treatment, which the pharmaceutical

“Most manufacturing problems would be avoidable if a firm simply invested adequate resources to improving its facilities and procedures.”

–Harvard Law School Analysis (2012)
industry manipulated to maximize financial returns at the direct and predictable cost of patient’s well being. It is a good example because it has been in use for many decades, and thus no current company can claim the need to recoup R&D expenses. It is also a good example because its story involves several pharmaceutical companies over a period of years, and thus exemplifies a common practice. As such, it seems reasonable to take this example as bearing the industry’s imprimatur.

In 2006, Mustargen was produced by Merck Pharmaceuticals. According to reporting at the time, Merck wanted to raise the price, but the company’s highly visible public image made such a move undesirable [7]. Merck sold it to Ovation Pharmaceuticals, a small company, thus without such concerns. Ovation raised Mustargen prices 1000%. Merck continued to manufacture the drug; Ovation merely purchased and resold the finished product [7]. In March of 2009, the FTC approved the purchase of Ovation by European giant Lundbeck for $900 million. In a March 19 press release, Lundbeck stated:

“Today’s announcement will not affect or interfere with any product availability or support for any of the products that Ovation currently has on the market.” [53]

By early September 2010, the FDA had listed Mustargen as in short supply. Nearly two years later, on November 5 2012, the FDA relisted the shortage as “resolved.” At that time, Lundbeck made the following public statement:

“[We are] pleased to announce Mustargen is once again available in the U.S….We’ve worked closely with the FDA and invested significant resources [in] a state-of-the-art facility that will help enable a consistent, reliable, long-term source of product…Thank you for your patience…We are very pleased to once again be able to make this important therapy available to your patients.” [54]

But the sentiment of that statement was short lived. On December 14 of that year, just 39 days after Lundbeck praised itself for creating a “consistent, reliable, long-term source of product,” [54] the companies sold Mustargen to Recordati Rare Diseases; another company with a history of employing purchase/price-hike tactics [55]. Since Lundbeck’s reference to manufacturing capabilities is instructive to investigate. As has been cited previously, the causes for drug shortages have been described as “complex.” In fact, the GAO’s November 2011 Drug Shortages findings, after separating external factors such as raw material shortages, divided the causes of drug shortages into the following three categories:

1. Temporary manufacturing shutdown to upgrade an entire facility.
2. Temporary manufacturing suspension of a particular drug to investigate or resolve a manufacturing problem.
3. Unspecified manufacturing delays [56].

As noted, visibly absent is any attribution of drug shortages to business decisions. However, it is notable that the reasons cited all relate to the means by which sales of blockbuster drugs can increase; all relate to capacities of production. This is, in essence, correct, because the FDA gives permission for a particular manufacturing line to produce a particular drug, so that product production cannot be shifted around to accommodate shortages without changes to the FDA production specifications. These reasons, and those offered by Lundbeck, are written in the language of production, and while they are intended for use by patients, that is not the mindset of those who show up for work at Lundbeck every day. They are, as Lawrence Perkins argued, there to make money, not to save or better lives. A 2012 Harvard Law School analysis of drug shortages concluded:

Although it is tempting to view manufacturing problems as an independent cause of shortages, the more likely story is that manufacturing problems are just a consequence of another underlying cause. [57]

And in the case of Lundbeck and Mustargen, a review of Lundbeck’s financial reports reveals a statement discordant with the sentiment expressed just over a month prior, but consistent with their values and duties to their stockholders:

“…Some of our products are maturing, and we are addressing this challenge by focusing on our pipeline, partnerships and new product launches… Our new products generated total revenue of DKK 2,141 million, which is more than we lost on the patent expiration of Lexapro in the US…”[58].

“...There is some evidence of the profit-dependence of manufacturing prowess.”

–Harvard Law School Analysis (2012)
"Maturing," is industry speak for heading “out of patent,” a condition also known as “loss of exclusivity” (LOE). In essence, this means the company’s product is at risk of facing competition in the marketplace. It is notable that the free market is the very thing industry defenders point to when arguing government regulation is not necessary; free markets are, according to this line of argument, “self-regulating.” [17, 59] But the evidence shows that two things pharmaceutical companies eschew are risk and competition.

Being out of patent is a decidedly undesirable state of affairs for a pharmaceutical company. Consider: analysts predicted that when Pfizer’s cholesterol fighter Lipitor came out of patent in 2010, the company’s revenue stream would be slashed by 25% by 2015. In few industries are there businesses that rely on a single product for 25% of its revenue. Financial reporting of Lundbeck and other companies show an increasing trend towards focusing on new drugs [16]. Unless manufacturing facilities are expanded to do this, something has to give, thus creating “orphan” drugs and drug shortages [60].

Pointedly, sterile injectables, touted as difficult to manufacture, are rarely unavailable in brand formulations according to the U.S. Department of Health and Human Services, which also found the same relationship holds for even new, never before manufactured drugs—if they enjoy patent protection or other market exclusivity arrangement [61]. Moreover, the Harvard Law School analysis noted the common sense response to ‘manufacturing issues’ as causally determinant:

Most manufacturing problems would be avoidable if a firm simply invested adequate resources to improving its facilities and procedures. [57]

Concluding:

“There is some evidence of the profit-dependence of manufacturing prowess.” [57]

However, whether difficult to manufacture or not, sterile injectables do suffer one logistical hurdle that seems to significantly affect their availability in generic form; they are “just in time” drugs, meaning they must be manufactured and used quickly because they have an inherently short shelf life [57,21,22,62]. The inability to store these medications means a manufacturer must estimate the production volume, knowing surplus will go unused, and thus unremunerated.

Finally, drugs that are unavailable in one market are often available elsewhere [63], but before you consider traveling to obtain treatment, known as “medical tourism,” some locations require residency to purchase the drug.

The Case of Turing Pharmaceuticals
The issue of drug shortages cannot be evaluated without evaluating the business calculations that comprise industry strategies. Turing Pharmaceuticals is a case in point, for while extreme, it exemplifies a growing trend among many pharmaceutical companies in which the public interest is completely subverted for the pursuit of profit at all costs. Consider former CEO of Turing Pharmaceuticals Martin Shkreli, who infamously increased the price of a single pill of the 62-year-old drug pyrimethamine (Daraprim) from $13.50 to $750 in 2015, a more than 5,000% increase [64]. This captured the attention of Congress, and preceding congressional hearings ranking Democrat on the House Committee on Oversight and Government Reform Rep. Elijah Cummings (MD) summarized key findings in two released memos. Among the findings drawn from 250,000 pages of documents from Turing Pharmaceuticals was evidence of a business model built around buying particular medications for which there were no alternatives and hiking the prices sky high [65-67]. In a separate report released by Senators Collins (R-ME) and McCaskill (D-MO) found four companies, Turing, Retrophin, Rodelis, and Valeant, all engaging in a business model that enabled them to identify and acquire off-patent sole-source drugs over which they could exercise de facto monopoly pricing power, and then impose and protect astronomical price increases [65]. The business model consists of five central elements:

1. **Sole-Source.** The company acquired a sole-source drug, for which there was only one manufacturer, and therefore faces no immediate competition, maintaining monopoly power over its pricing.

2. **Gold Standard.** The company ensured the drug was considered the gold standard—the best drug available for the condition it treats, ensuring that physicians would continue to prescribe the drug, even if the price increased.

3. **Small Market.** The company selected a drug that served a small market, which were not attractive to competitors and which had dependent patient populations that were too small to organize effective opposition, giving the companies more latitude on pricing.
4. **Closed Distribution.** The company controlled access to the drug through a closed distribution system or specialty pharmacy where a drug could not be obtained through normal channels, or the company used another means to make it difficult for competitors to enter the market.

5. **Price Gouging.** Lastly, the company engaged in price gouging, maximizing profits by jacking up prices as high as possible. All of the drugs investigated had been off-patent for decades, and none of the four companies had invested a penny in research and development to create or to significantly improve the drugs. Further, the Committee found that the companies faced no meaningful increases in production or distribution costs.

Manufacturer consolidation, drug shortages, and monopolistic tactics that limit competition create fertile ground for predatory pricing [68]. This business model leverages two key factors: first, since the drugs were not invented by the company there would be no costs associated with R&D, and second, because the target drugs were needed by patients to survive, and no alternative therapies of clinical equipoise existed, demand would be inelastic [66]. Therefore, price elasticity, which is almost always negative, would remain at approximately one; as prices rise, demand does not decline, as it typically would when governed by the laws of supply and demand.

Price hikes could be steep and made with impunity; revenue, rather than decreasing as demand drops, would simply increase as well. As the deal for Daraprim was closing in May of 2015, Shkreli wrote in an email to the chairman of the board:

> “Very good. Nice work as usual...$1bn here we come.” [69]

Shkreli also wrote in August of that year that the price hike would bring in $375 million per year for three years, “almost all of it profit.” [69] Documents from Turing Pharmaceuticals show skyrocketing drug prices were part of the plan from conception. Turing Pharmaceuticals anticipated that HIV patients, who are particularly in need of protection from infection, could be, the company opined, s problem by virtue of their strong and public advocacy. Turing’s plan was to mollify backlash through misdirection and obfuscation. Shkreli pointed to coupons, patient-assistance programs, and discounts, as evidence the company was committed to making sure the medication was available to the patients who needed it; meanwhile they increased the prices orders of magnitude and hid the real cost from the public—as had been the plan from the beginning. While patients did not pay full-price for the drug, reporting by the *Chicago Tribune* revealed some patients still ended up with $6,000 copays, and at least one patient having a $16,830 payment [69].

However, while this trend is expanding in the industry, some groups are fighting back. Bloomberg recently reported on the pharmaceutical lobbying group Biotechnology Innovation Organization’s (BIO) new “Costs in Context” initiative, which is directed specifically at distancing its members from the likes of Turing. It points to PhRMA infographics that highlight facts that cast the industry in a positive light, but those facts are highly selective [70, 71].

**Axiological Assessments and Ethics**

These are but a couple examples of a troubling trend. As *New York Times* reporter Alex Berenson noted in 2006:

> “people who analyze drug pricing say they see the Mustargen situation as emblematic of an industry trend of basing drug prices on something other than the underlying costs. After years of defending high prices as necessary to cover the cost of research or production, industry executives increasingly point to the intrinsic value of their medicines as justification for prices.” [7]

Berenson is observing an axiological shift within the pharmaceutical industry, or at least as a marketing effort, and one borne out in fact: Premier found the highest marked-up drugs were ones needed to treat critically ill patients [21]. The observation posits a change in how medications should be evaluated in determining their worth—rather than be evaluated by the traditional costs of production, lifesaving drugs should be priced according to their “intrinsic value.”

In this setting, the intrinsic value of a drug can mean only one thing, its value to the patient who needs it to survive. Even the Bloomberg reporting referred to above refers to the “profound value” to patients, [70]. Seeing families of very ill children every day, there is no doubt that most or all of them would give everything they have to save the life of their child; many do precisely that. So let us tentatively accept the intrinsic value of many of these drugs can end up in some sense equaling the lives they save—that is the opportunity cost of going without them—is this the correct way to assess their economic value?

Two lines of argument address the notion of drug value as an axiological question. The first is a
categorical argument. In general, something is said to be *intrinsically* valuable because it has value in and of itself, just by virtue of existing. Something that is valuable only in relation to something else, that is, valuable because it is needed to effect some goal or end, is said to be *instrumentally* valuable; it is an instrument to be used to do or obtain something else.

Drugs, in and of themselves, have little or no intrinsic value; it is patients needing the drug that instantiates its value, because it is a means to health, pain relief, etc. No one will buy my $1,000 vaccine for the Purple Death because there is no such thing as the Purple Death. I probably could not get $1 for it because its only value is its utility to achieve some end. People, however, have intrinsic value; parents see their children as valuable because they exist, not what they can do. If person B needs compound A to live, and B is valuable in and of herself, whereas A is valuable only insofar as B cannot live without it, the only rational course of action is to give A to B. We might say B *should* have A.

A natural response is that A has other, *attributive* values; it is comprised of materials whose purchase costs money that allows others to sustain themselves and their families, and its production provides jobs upon which still other people rely to support themselves. That proposition can be justified on social contract grounds. However, doing so merely reinforces the claim that financial value of lifesaving drugs is properly understood in terms of the traditional costs of production Berenson referred to; the claim that medications have intrinsic value fails on the grounds that A has no value in and of itself. Importantly, the proposition that drug price should be parameterized to the value of the life it saves succeeds in one important respect: it denudes its *direct parallel* to ransom.

The other type of argument is best understood historically. It is therefore instructive to step back for a moment once again and look at medicine in general in the United States. American medicine developed into a profession with unusual independence from outside regulation, precisely what Big Pharma says it wants [25, 34-37, 72]. It has been argued that at least part of that independence, perhaps a great deal, stems from physicians, as a profession, adopting a fiduciary duty to their patients [37, 13]. The longstanding practice of physicians not patenting therapeutic interventions (as was common in dentistry) is one example, and modern clinical bioethics provides others in the institutionalized values of *beneficence, non-maleficence, and respect for autonomy* [73]. This has resulted in a field of endeavor in which practitioners have unusual latitude and discretion [37, 94]. Paul Starr goes so far as to use the word *sovereign* to describe the profession in his Pulitzer Prize-winning book, *The Social Transformation of American Medicine* [37]. For the sake of both brevity and clarity, I will refer to the overall disposition towards patients as derivative of the physician’s fiduciary duty, understanding that duty has a specific definition and intended use. Nonetheless, I feel the disposition I refer to is roughly encapsulated in the term.

Starr begins with an examination of what it means for something or someone to have *authority*. He points out that authority is related to control, and thus has a relationship to power, but argues, as Hannah Arendt does, that exercise of power is paradoxically a failure of authority [37, 10, 74]. Authority, “incorporates two sources of effective control: *legitimacy and dependence*. The former rests on the subordinates’ acceptance of the claim they should obey; the latter on their estimate of the foul consequences that will befall them if they do not.” [37, 10] Medical care derives its legitimacy from its results, but not its results alone; even when results are poor, patients are willing to believe physicians are legitimate, merely unsuccessful, or unhelpful. A key component has been that in the United States, efforts of physicians to arbitrarily increase the rates they charge for the care they provide have historically been met with both public outcry and governmental intervention. Starr notes:

“A series of legal decisions shortly after the turn of the century effectively precluded the emergence of profit-making medical care corporations in most jurisdictions. Between 1905 and 1917, courts in several states ruled that corporations could not engage in the commercial practice of medicine, even if they employed licensed physicians, on the grounds that a corporation could not be licensed to practice, and that commercialism in medicine violated “sound public policy... These decisions were not models of rigorous legal reasoning... Respectable opinion did not favor “commercialism” in medicine.” [37, 204] The latter point is important; while special interests undoubtedly have profound influence, a society’s values as a whole include ethical values [1, 6]. Governmental regulation requiring labeling, safety testing, and the like have saved the pharmaceutical industry from itself, and as Starr notes, when the medical profession has strayed from its central duty, society has corralled it back in.
Competing Fiduciaries
Nonetheless, pharmaceutical companies’ fiduciary duty is understood as to their stockholders, rather than the patients who rely upon their products to survive. The ethical issue is, at its basis, an assessment of whether these two fiduciary duties can meaningfully coexist as increasingly pharmacological interventions become standard of care, and whether the fiduciary duty to stockholders is justifiably absolute in the way the fiduciary duty to one’s patient is.

It should not be forgotten that most medications were developed at some point with public funds; roughly 75% of new molecular entities owe their existence to NIH funding [75]. Traditionally, acceptance of public funds has come with certain responsibilities. Such funding wasn’t made available by the government to make enterprising individuals rich, or even find the new discoveries or forge new interventions; public funding is made available for the purpose of bettering the public good. One could say the government has a financial fiduciary duty to its citizens, which in the framework of the values the pharmaceutical industry endorses, would dictate reigning in what Big Pharma can do so as to provide a better return to the citizens.

It is also not at all clear that the wealth of the entrepreneur is a necessary component of that process, as one can imagine a non-profit pharmaceutical company just as easily as a group of physicians volunteering their skills. Rather, it seems that the use of public funds to develop marketables that end up in the hands of Shkreli and others like him is proof that reform is needed, and justified by having furnished the means of development to begin with. It also appears this can be validated without resort to bioethical values; the industry’s own values suffice.

Given this, it seems some form of government intervention not only necessary, but justified. Physicians have been largely self-policing, and thereby escaped the bureaucratic infiltration of regulatory frameworks present in industries such as banking and stock trading. The pharmaceutical industry, by both their historical actions, and the increasing degree of harm rendered by unethical practices—that thus far have no legal remedy—seems overdue for reconsideration.

There have been many proposals regarding how to improve the pharmaceutical industry. Some options include encouraging the insurance companies to pay higher prices for drugs that treat rare conditions, or subsidizing those that have little prospect of financial return. Some have already been legislated: while the Bayh-Dole Act allowed private corporations to patent publicly funded research, it also gave the government the power to cap prices—a power hasn’t exercised on even a single drug [75].

Perhaps the best place to start is the creation of a fiduciary duty to the patient that follows all work done with, or made possible by, public resources. Some mechanism is needed by which decisions made regarding drug production and pricing are based not solely on a (financial) fiduciary obligation to stockholders, but on the medical profession's fiduciary duty to patients. There was a time when physicians, as a group, were able to reign in the excesses of the pharmaceutical industry, and require ingredients be disclosed, and direct advertising to patients stopped [37][127][140]. A contemporary effort of the like seems overdue.

And while the pharmaceutical industry lacks the social authority that undergirds medicine, and thus lacks the foundation of trust medicine enjoys, medicine would do well to countenance the inversion of that state of affairs; insofar as it flirts with disestablishing its fiduciary bindings, so too may its authority wane.

Endnotes

64. Freundlich N. Keep the focus on rising drug prices, not smirking Shkreli (February 6, 2016). http://reforminghealth.org/2016/02/06/keep-the-focus-on-rising-price-drug-prices-not-smirking-shkreli/ Accessed 2016 Mar


Students rush into the halls to watch another fight. While some hoot and holler, others whisper, “they belong at Hartgrove.” As the dust clears, students are escorted back to their classrooms, and I ask my 8th graders about Hartgrove. They respond with a chorus of “that is where crazy kids go.” And thus was my introduction to adolescent mental health services as a teacher in the south side of Chicago. In actuality, Hartgrove Behavioral Health System is an inpatient psychiatric health service for children, adolescents, and adults in the Chicagoland area. After further questioning, I learned that students unable to be controlled by their guardians and schools are sent to Hartgrove in hopes they would be rehabilitated and acclimate back to the school community. These students are then connected to school social workers and counselors in hopes that services offered a few times a month would be enough to help the students’ mental health problems.

In theory, such programs are admirable; however, in practice they are not nearly adequate to treat the massive amounts of grief and instability my students face. What they need are easily accessible physicians that are able to provide consistent care for common mental health issues.

Fast forward a few years. I am now a pediatric resident in the very same community in which I used to teach. The mental health needs are no different, and the reality is that only about 15%-25% of children and adolescents who require specialty services actually receive them. Of that percentage, the retention rate is below 50% due to lack of transportation, financial constraints, stigma, or shortages of providers. Primary care providers, who provide over half of the mental health services in this country, have seen their ability to contribute to the mental health of our youth “carved out” by managed care organizations (MCOs),
who only use contracted behavior specialists, having deemed pediatricians ineligible to be compensated for mental health services they provide in their office [6]. The result is that primary care physicians, often the most appropriately suited to take on these matters, are left unable to treat the whole patient, body and mind.

In the last 4 decades, the role of the physician has changed considerably. In the words of Eric Cassell, physicians have gone “from treating patients to making treatment decisions.” Cassell states:

> To a medicine guided by marketplace principles and the socially based ethics of justice, the loss of the personal is irrelevant. The classical norms of clinical medicine—dedication to the patient, constancy, thoroughness, self-discipline, compassion—are not about saving lives and improving overall health; they are about this patient’s life and health [7].

What used to be a sacred bond between patient and provider has quickly become a rigid assembly line, ruled by protocols and flow sheets. Being able to treat the whole individual, body and mind, involves more than just the proper images and medications, but understanding the intricacies of relationship building. Patients are asked to reveal the darkest, most painful elements of themselves to their providers, often without any rapport established, even in life or death decisions. It is in these moments where we have failed our patients.

### The Problem

For many of my patients, treatment cannot be divided between physical and mental; issues overlap, and are intertwined, exacerbated by the fact that this is a disadvantaged population that is both traditionally underserved, and suffers mental health problems endemic of their damaged socioeconomic surroundings, and the attendant sequelae thereof [8].

As a result, physicians are often unable to meet their obligation to treat their patients in accordance with their fiduciary obligation to them. If I defer treating my patient’s mental health issue because of MCO strictures, knowing she will not, or cannot, seek out the services of a specialist, I am clearly not treating her healthcare needs as paramount. The actions MCO’s have taken in this regard deny these patients the rights they have been guaranteed through countless declarations of human rights, and such actions are at best an incompetent use of what funding is made available, and at worst, unjust. These actions also represent the continuing decline of the traditionally held conception of what a physician does, principally in terms of individuated and thorough care of a specific patient [9].

MCO’s purportedly exist to make needed healthcare services available to patients, but the problems with mental health service delivery in my community highlight an unacceptable failure to do so. It is irrational to allow the means of service delivery to compromise the service itself. MCO architecture has overridden the primacy of patient care, and as physicians, we have an ethical obligation to meet our fiduciary duty to our patients; we must act, first and foremost, in their interests. This is not so much a clinical problem as it is a policy problem, and corrective efforts will have to be made in that arena. However, I would like begin by highlighting some of the clinical issues I see before turning to that larger question.
a physician’s obligation extends beyond the clinic, to include advocacy for our patients.

A Few Examples
How are students and patients actually being let down? Consider Kimberly. Kimberly was a hardworking, mature 8th grade student, raised by an equally hard working single mother. She was a true leader, and often kept the class calm and together, not getting sidetracked by the temptations of the neighborhood. The first time she walked into my classroom crying and complaining of headaches, I knew of no other solution but to allow her to rest her head and offer to visit the school nurse. As time progressed and I came to know her better, I learned that her father would cancel visitations with her frequently, which resulted in headaches that would last through the next day. We would learn to cope with such disappointments together over next 2 years. Or Shannon, a quiet, 7th grader who treated all adults with respect, and who was committed to doing well in school. Her most impressive trait, however, was her ability to remain focused in the midst of everyday middle school drama. Thus, it came to everyone’s surprise when she broke down crying profusely after lunch one day. When finally calmed and in a safe environment, she revealed that she had seen her grandmother being shot in their home.

These were but a couple of the stories that highlight the issues my students shared with me in their journals every day while I was teaching. While reading such stories left my heart broken, I was limited by the amount of support that I could provide as a teacher. I was left trying to navigate a system that systematically left my students to fend for themselves. Where could they turn when our conversations and journal entries were not enough? Where could they find providers who were able to meet with them on a consistent basis, and help them through the resultant mental health strain imposed by their lives’ circumstances?

Primary care physicians, who may have once been able to provide that level of care, are no longer able to as MCOs continue to silo mental health care services. And while studies show that living in poverty imposes such a large cognitive burden that little reserve is left to focus on anything else, we ask the urban poor to pick themselves up by their bootstraps through academic excellence [10].

Now, as a physician, I find myself limited in my ability to help that same community. Jacob, an 8th grade student admitted to the hospital yet again as he jumps from one foster home to another, unable to manage his insulin for his type I diabetes. When finally granted the opportunity to spend a few minutes in his room, I can visibly see the pain he experiences from lacking consistent guardians who could help him with the medication regimen. With additional support, we could save him trips to the hospital, and ultimately save his life.

Or Samantha, a high school student who has missed months of school and numerous doctors’ appointments as her family battled homelessness. While I could care for her acute healthcare needs, I was left feeling helpless about the myriad of social determinants of health that were contributing to her physical decline.

And yet, standing before me, I see that the enormous challenges and trauma that members of this, and other similar communities face are given little acknowledgment. When our patients fail to take medications, no-show on their appointments, or suffer from mental health instability, they are deemed as lazy or even as “crazies.” Yet MCOs continue to require physicians to see more and more patients, and utilize non-physician providers, barring physicians the time to establish a holistic understanding of the complex mental health problems that may be hindering our patients to thrive in school and home [11,12].

There are three broad components contributing to the problem outlined above. Each will be discussed in turn prior to advancing the general thesis that as physician’s obligations to individual patients have been in decline over the past several decades, our current obligations must extend beyond the clinic, to include advocacy for our patients if we are ever to recapture our role as treating the whole person.

Cultural Components
There is little acknowledgment by society, or even the medical community, of adverse childhood experiences (ACEs) being a contributing factor to the physical health problems that we seek to manage, as found in the monumental ACEs study by Kaiser Permanente in 1998 [13]. Instead, society continues to carry a notion that people should succeed regardless of the upbringing or past hardships. And as a medical community, we go about treating sexually transmitted diseases, managing obesity, and providing anticipatory guidance without an adequate understanding of the stories of abuse and household dysfunction that children live with on a day to day basis. Instead of embracing mental health problems as another serious health condition, we label such patients as difficult or hopeless [14].
Maybe such misguided attitudes are rooted in our own discomfort in dealing with such issues, given many of our backgrounds are in cultures and communities that stigmatized mental health problems [15,16,17,18]. For example, in the Asian Pacific Islander American (APIA) community, patients often seek treatment as a last resort, and only after the mental health condition has caused serious harm for the patient, family, or community. The notion that mental health problems are a byproduct of not being resilient enough, and that hard work and willpower are all that is needed to overcome such problems is a pervasive misconception [19,20]. The stigma associated with seeking professional help continues to be a major roadblock, and patients will often turn to family, friends, and clergy before seeking out counselors or therapists [21]. Such upbringing contributes to a culture of health care workers, many of whom under-recognize mental health problems, and patients who underreport the toll mental health problems can have on overall wellbeing [22].

Commercial Components
MCOs are structured in a way to incentivize cost effective medicine and limit variation in clinical practice patterns. Health care efficiency means creating the best health outcomes with the least amount of dollars spent. In theory, this is a noble and just endeavor; however in practice, it leads to increased pressure to do more with less, which means less time spent with patients, utilizing therapies that may not be most therapeutic, but are most cost effective; and juggling what tests and treatments will provide the most utility. Instead of using our clinical judgment, we must now consider monetary incentives/penalties and pressures from peers and supervisors in our decision-making. Such structures are bound to compromise patient care and advocacy for cost savings [23].

The MCO health care system today prevents physicians from treating the entire human being, as they struggle with the mammoth task of plugging patients into adequate treatment modalities. For instance, primary care physicians are faced with the reality that primary care visits last an average of 13 minutes, addressing roughly six patient problems in that time span, including mental health problems [24]. It is unrealistic to expect that an adequate amount of time can be committed to treating mental health problems, yet studies show that patients with mental health problems want more primary care involvement in their treatment, as they have often formed strong patient-provider relationships and see it as way to avoid the stigma of seeing a psychiatrist [25].

Further, payment for office visits with a mental health diagnosis code has traditionally been discounted by Medicare and Medicaid for primary care. This policy disproportionately affects the patients in this community, which contain large numbers of traditionally underserved groups such as poor, ethnic minorities, who often seek care for mental health problems from general medical providers [26]. In doing so, MCOs have effectively denied these patients’ rights to access equitable, holistic health care and prevented providers from doing what is best for these patients.

In contrast to a primary care appointment, a psychiatric visit usually lasts around 30 minutes to 1 hour, and focuses on a singular problem. Access to a psychiatrist is often only offered to patients with private insurance. This limitation partitions off many of the patients in this community who may benefit from such services the most. Even insured patients are seeing their level of mental health coverage being slashed by employers and insurance providers, with most plans having maximums on outpatient visits and inpatient hospitalization days.

Political Components
And yet, government funding for mental health services continues to be on the decline, making access that much more difficult. In 2012, then Illinois Governor Patt Quinn closed two state run mental health hospitals and cut over 100-million dollars from the state’s mental health funds [27]. Soon thereafter, the Mayor of Chicago, Rahm Emmanuel, closed six of the 12 city
run mental health clinics in poor and crime-ridden neighborhoods [28]. Both city and state officials cited budget crises as the reason as to why such services were cut; however, such actions demonstrate the low priority of accessible mental health services in our city and state.

Things have not improved much with the new Governor, Bruce Rauner, as the state has gone one year without a passed budget, resulting in organizations that receive state funding feeling the pinch. While some clinics have been able to stay afloat through tapping lines of credit, others have had to close their doors. In fact, from 2009 -2012, Chicago cut $113.7 million in funding for mental health care services, which is the 4th highest in the nation by percentage [27]. If we are to truly advocate for our patients, we must stand against such injustices that affect the most vulnerable communities through the ballot box and lobbying. It is not enough to patch holes of health once they are created; we must prevent such holes from forming in the first place by engaging in activism to change the social, economic, educational, and political system to ameliorate suffering and contribute to human well-being [28].

Implicit Obligations: Agency and Activism
Pediatricians do not choose the profession; the profession chooses them. It is anathema to say, “the MCO’s have made it impossible for us to treat the whole patient, so we have no obligation to do so”, and rest easy. In my mind, our obligation remains. As pediatricians, we have the obligation to treat more than just physical ailments; we have an obligation to relieve suffering, which for communities such as mine necessarily includes treating the whole person, body, mind and spirit. Consider: Is it in line with the concept of beneficence, taking actions that will benefit the best interest of patients, to partition off mental health care in the manner described, if in doing so we deny them access to the care they need the most? How can we see ourselves as patients’ fiduciaries when we send them off with a referral to a specialist we know they either will not, or cannot, see? How is that any different from performing a useless test?

While it could be argued that the divisions in who provides what care should be a clinical decision, or at least a determination based on clinical evidence, it is not. Meeting our obligations as physicians and as clinicians, and upholding the ethical principles of providing quality patient care are tied to policy-level decision-making where there is no fiduciary duty to patients. That requires our involvement in an entirely different arena of practice. We must promote mental health through community organizing, advocacy, and legislation. In doing so, the medical community can work in unison with insurance companies and politicians for the betterment of the individual lives of patients, and the communities they live in. They deserve adequate food, safe neighborhoods, good schools, and have a right to high quality health care. What does high quality medical care mean without these things?

In “Perspective: agency and activism: rethinking health advocacy in the medical profession” Sarah Dobson and her colleagues argue that:

...while physicians recognize advocacy as an essential domain of competent and responsible practice, there is little clarity around what a physician should do as a health advocate and how this should manifest in daily practice. Further, Dobson and her colleagues differentiate agency as advancing the health of individual patients; and activism, as advancing the health of communities and populations. This distinction is useful in the present discussion of mental health care in the MCO setting because it clarifies the roles physicians have. As agents, in clinical, one on one interactions physicians can work the system for their patients, which is in keeping with our fiduciary duty. However, agency only goes so far. In order to make greater change we must engage in health care advocacy, using our expertise to push for social, political, and ultimately commercial changes [29].

Such thoughts are in line with the AMA Declaration of Professional Responsibility: Medicine’s Contract with Humanity, which state that as physicians, we are bound in our response to human suffering by applying our skills and knowledge, beyond the traditional patient-physician relationship, to care for the sick and the suffering. It is not our specialty that determines which patients we will treat, but rather humanity itself is our patient [30,31].

Joshua Freeman draws on Dobson’s distinction and argues agency is not sufficient if physicians want to have the greatest impact on patient’s health. He points out that while agency is accepted as a medical obligation, advocacy is less accepted, often considered to be outside of their professional responsibilities or lost in the long list of tasks that physicians must complete day in and day out [32].
However, how can the actions that make the most impact on health be outside the responsibility of those persons who are dedicated to that very thing? It, of course, cannot. From a Utilitarian perspective, advocating for our patients’ best interests is an obligation precisely because it can have such an impact. The greatest good is clearly served by physicians working as advocates in this manner, where potentially all patients can benefit from changes inspired by those who have the specific expertise necessary to know what needs to be changed. To not act in a manner that maximizes the good for the largest number of people is not ethically permissible, and thus advocacy is an ethical obligation for physicians.

From the Kantian perspective, generalizability and universalizability are the critical components of ethical maxims. It is not sufficient for a maxim to just treat people as ends in themselves; the maxim must be as general as possible so that it can guide us in as broad a set of circumstances as possible, and it must also be universalizable to all similar people in similar circumstances \[33\]. For physicians, treating our patient’s ailments is an ethical maxim; partitioning off the role of advocacy lessens the generalizability of the maxim. Alternatively, arguing certain physicians are responsible for advocacy, while the rest are not, lessens the universalizability of the maxim. Therefore, advocacy is obligatory from this ethical perspective as well.

As physicians, we have an obligation to treat our patients, both physical and mental ailments, both inside and outside the clinical setting. Unless we are able to do so, and not be stymied by MCOs or other insurance companies, we will not be able to meet that obligation. Thus, we must continue to fight for the rights of our patients through advocacy and activism. I push on as I think of Kimberly, Shannon, Jacob, and Samantha.

Endnotes
6. American Academy of Child and Adolescent Psychiatry Committee on Health Care Access and Economics Task force on Mental Health. Improving Mental Health Services in Primary Care:
From July 7 through July 9th 2016, the Harvard Center for Bioethics held its annual Harvard Clinical Bioethics Course at the Harvard Medical School in Boston. Nearly thirty hours of lectures, discussion groups, working lunches, and even a play were presented over those three days, all aligned with conveying the principles of good clinical bioethics, and discussing the emerging issues in the profession to the students in attendance.

The staff and speakers, led by Christine Mitchell RN, MS, MTS, the center’s Executive Director, and Robert Truong MD, the center’s Director, gave presentations and facilitated talks on the development of clinical bioethics, the philosophical underpinnings of moral reasoning and ethical justifications, schools of ethical thought, consultation standards, competencies, and the future of clinical bioethics. Having attended the course this year, I thought it might be helpful to share what the program had to offer, and what I learned.

The Harvard Bioethics Course is designed as an academic all-you-can-eat buffet; twenty-eight individual sessions, running from 8:00AM through 6:00PM or later, every day for three days. The course was organized around sixteen lectures that all students attended, broken up midday by “box lunch” discussion groups that students selected, and mid-afternoon by concurrent sessions, also student selected. Concurrent sessions addressed specific subject matter such as issues in maternal fetal medicine, pediatrics, behavioral health, women’s health, genomics, neuroethics, professionalism, medical futility, advanced care planning, and medically assisted dying.

For someone not familiar with the subject matter, the course would be a lot of work, but not inaccessible to those who have a cursory background in the material and are willing to put in the time to do the extensive reading prescribed. A number of participants were members or chairpersons of their institution’s ethics committee, and many of those were laypeople working outside of medicine. Others were longtime practitioners of clinical ethics consultation, including physicians, nurses, philosophers, and chaplains, wishing to know more, or hone the skills they have.

The course struck a good balance between general introduction and rigorous treatment of subject matter; Patrick Smith, Charlotte Harrison, Frank Chessa, and
Rebecca Brendel provided introductions to, respectively: Principalism, Narrative Ethics, Consequentialism, and Virtue Ethics, in 15-minute blocks. Andrew Schroeder’s lecture on moral reasoning and ethical justification methodically proceeded as a step-by-step tutorial on the mechanics of one form of argument justification, using serial hypothesis testing, and one type of principle building through the analysis of the familial resemblances among two sets of propositions. By taking what is often an abstruse subject in professional philosophy and making it specific and concrete through step-by-step examples, Dr. Schroeder’s approach is one that will no doubt be emulated by students returning to their ethics committees. Robert Truog MD rounded out the first day with a lecture on medical futility.

Day two began with Lachlan Forrow, MD’s lecture Atoms, Autonomy and Molecular Ethics. Edward M. Hundert, MD then addressed a common issue faced by ethics program directors, in his lecture, Teaching Bioethics: Practical Approaches to Common Challenges. Andrew Schroeder returned with a session on Rationing and Distributive Justice, and the morning sessions ended with Carrie Blout, MS, CGC presenting Ethical Questions in the Genomic Era.

Following the Concurrent Sessions, former New England Journal of Medicine Editor, Marcia Angell MD, delivered a talk on Medically Assisted Dying: Facts and Values. At once both practical and perpervid, Angell’s lecture was easily the most controversial of the course, opening a discussion in which, in a single room, one witnessed dispositive salvos volleyed across professions, borders, and beliefs; an Australian physician’s prophetic fears were met with first-hand Swiss and Belgium experiences; European, South American, and Japanese sentiments were shared, along with multiple appraisals of the issue from different schools of ethical, political, and social thought. The debate had the feeling of a mini-United Nations, albeit more collaborative and congenial.

Closing day two, Lynn Bush PhD, of Columbia University’s ethics program, took a different approach to a lecture, and instead staged a play, “Genomics in Play: DNA Dialogues and Ethical Dilemmas,” a didactic dramatic vignette. Dr. Bush infused the dramatic and serious aspects of the issue with a bit of comedy by playing the dialogue of each character off of the personalities of the actors playing those characters. This not only made the play fun to watch, but impossible not to pay close attention to, thus driving the message home. The play was followed by a panel discussion, with the actors serving as the panel, fielding questions and comments from the audience.

If there had been a theme of the course, it was where the standards and competencies of Health Care Ethics Consultation are taking the field. While these standards have been enumerated by the American Society of Bioethics and Humanities (ASBH) Standards and Competencies, most recently updated in 2011, their normative nature, not to mention that of the subject matter itself, leave the issue of what to do with such standards hotly debated. Martha Jurchak went through the Standards and Competencies, Christine Mitchell discussed preparing a portfolio of ethics consultation cases and the structuring of ethics committees and consult services, and Jennifer Kesselheim provided insight on how data inform the practice of ethics consultation, showing the state of ethics consultation data collection is, in general, lacking. Holly Lynch covered what ethicists should know about the law, and Robert Truong addressed what to do when things go wrong (iatrogenesis), focusing on talking with patients after medical mistakes.

In box lunch sessions, attendees shared their experiences and institutions’ ethics consultation practices. While most attendees were from the United States, the course clearly has a global draw; students in attendance hailed from Australia, Europe, Japan, and the rest of the Americas. The students were diverse
While clinical ethics consultation recommendations are not binding, they nonetheless have influence; with physicians, nurses, hospital boards, and judicial processes, ethicists now occupy a space within the sphere of the healing enterprise, where involvement is usually restricted to those who have passed a rigorous, formalized licensing process with established criteria for inclusion. One proposed method that avoids the pitfalls of a standardized test is called “attestation,” which, in brief, one could obtain by submitting a portfolio demonstrating one’s experience leading ethics consults on a variety of different issues. This allows applicants to demonstrate results by a variety of means, and from a variety of viewpoints—necessary conditions for any systematic appraisal of value-laden content in our pluralistic multicultural society.

However, whereas a large medical center can have 300 or more consults per year, the number is 1/10 of that at even the largest pediatric institutions, and 1/100th, or about three consults per year, on average across all hospitals nationwide. This would relegate attestation vis-à-vis a portfolio of a dozen or more different cases available only to practitioners at the large, urban medical centers. Problematically, it is in such centers that ethics consultation is relatively well developed; yet most Americans receive their healthcare locally, through the 4,999 community hospitals, of which 1,980 are in rural areas, and 1,328 of those are critical access hospitals that have no more than 25 beds. Still, portfolio/attestation appears to be the most creative and flexible of the options currently available; certainly more so than any standardized examination process that currently exists.

Closing out the course, David Magnus, Editor of The American Journal of Bioethics, discussed the future of clinical bioethics. In Dr. Magnus’s view, ethics consultation will eventually become fully ensconced in the medical school/licensing apparatus. This is a controversial position, but nonetheless indicative of the fact that while clinical bioethics consultation has come a long way, it remains very much a nascent enterprise. It falls to those of us long, currently, or becoming involved, to shape this future.

Students review material between lectures in the auditorium.

**Concurrent Session Topics**

**Competencies for Ethics Consultation—Preparing a portfolio**
- Christine Mitchell, RN, MS, MTS

**Ethical Tensions between Maternal Fetal Medicine and Pediatrics**
- Stephen D. Brown, MD

**HMS Center for Bioethics: Educational Opportunities**
- Rebecca Weintraub and Brendel, MD, JD

**Pediatric Ethics: Medically Shaping Children**
- Judy Johnson, MA, JD

**Reason and Emotion in Ethics: Mind the Gap**
- Guy Maytal, MD

**Talking to Families about Ethics Consultation - A Video**
- Martha Jurchak, RN, PhD and Wendy McHugh, RN, MS

**Advance Care Planning: Legal documents to patient-centered process**
- David Sontag, JD, MBE

**Values Variability in Neonatal Nurseries**
- Bonnie H. Arzuaga, MD and David Urion, MD

**Microethics**
- Robert D. Truog, MD

**Professionalism, Ethics, and Behavioral Health**
- Stephen F. O’Neill, LICSW, BCD, JD

**Structuring Ethics Committees and Consult Services**
- Christine Mitchell, RN, MS, MTS

**Studies of Ethics Consultation: How do the Data Inform our Practice?**
- Jennifer Kesselheim, MD, MBE, MEd

**Students review material between lectures in the auditorium.**
A digest of recent clinical and academic work specifically relevant to pediatric bioethics and pediatric clinical ethics. The links to articles, books, and other references below are selected by our editors based on the materials’ potential interest to our readers. These materials represent a sampling of what is being published in the field, not as a ranking or endorsement of these materials others we may not have seen.

Readers may suggest materials for inclusion, provided those recommendations come from persons not associated with the research, writing, or publication involved.

Adolescents

Conflict of Interests

Conscience & Conscientious Objection


Smalling R, Schuklenk U. Against the accommodation of subjective healthcare provider beliefs in medicine: countering supporters of conscientious objector accommodation arguments. J Med Ethics. Published Online First: 31 October 2016 http://jmebeta.bmj.com/content/early/2016/10/31/medethics-2016-103883.info

Decision Making/ Uncertainty/ Nudges

Duty/ Virtues/Truth-telling

Ethics Consultation

Ethics Education


Human Rights

Infectious Disease/ Vaccinations/ Epidemics

**Misconduct Concerns**


**Moral Distress**


**Neonatology and Fetal Issues**


**Pain**


**Principles - Autonomy, Beneficence, Nonmaleficence, Justice**


**Professionalism**


Kerruish N, Anderson LC. It started with a kiss. *J Med Ethics.* 2016; 42: 638-639. [http://jme.bmj.com/content/42/10/638.full.pdf+html](http://jme.bmj.com/content/42/10/638.full.pdf+html)

**Rationing/ Denial of Coverage/ Allocation**


**Religion/ Spiritual Issues**


**Reproductive & Related Issues**


Mertes H. The role of anticipated decision regret and the patient’s best interest in sterilisation and medically assisted reproduction. *J Med Ethics.* Published online 10/7/16. [http://jme.bmj.com/content/early/2016/10/07/medethics-2016-103351? papetoc](http://jme.bmj.com/content/early/2016/10/07/medethics-2016-103351? papetoc)

**Research**


**Surgery**


**Technology /Social Media / EMR’s**


**Transplants/ Transfusions/ Tissue Donations**

Caplan A, Purves D. A quiet revolution in organ transplant ethics. *Journal of Medical Ethics.* Published Online First: 19 April 2017 [http://jme.bmj.com/content/early/2017/04/19/medethics-2015-103348](http://jme.bmj.com/content/early/2017/04/19/medethics-2015-103348)
