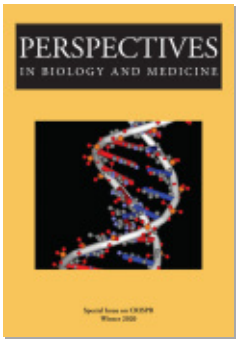
Billy Idol

Ethan J. Weiss



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ABSTRACT Ruthie Weiss was born with white hair, but her parents did not consider the possibility of there being more to the story until they noticed that she was not visually tracking when she was just a month old. Thus began a long and continuing story of the discovery of Ruthie's albinism, her significant visual impairment, but also her courage and determination to do anything and everything her peers do, if not more. But this story is really about how her parents grew to embrace the impact Ruthie (and importantly Ruthie's disability) had on their lives and the lives of everyone with whom Ruthie interacted. The experience of raising Ruthie ultimately led her parents to think about a world where she might not exist, or at least might not exist with albinism. But it also led them to ponder a future in which children with genetic differences like albinism are gene edited using technologies like CRISPR-Cas9.

Billy Idol was the name we gave Ruthie in the hospital in the days immediately after she was born. She had fluorescent white hair, and had she been born to different parents, they might have thought more of it. But both of Ruthie's parents had bleached blond hair as young children. So in the late summer and

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I want to acknowledge my wife Palmer for being a spectacular partner; I am fortunate and grateful to have had this journey with her. I also want to acknowledge my daughter Mina; our dog McDuff; the rest of our family and friends; and Ruthie's friends, doctors, teachers, coaches, ski guides, and all the other people who have helped her thrive in this world. Lastly, of course, I want to acknowledge Ruthie herself.

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into the fall of 2006, we happily celebrated the arrival of our second child, little blond baby Ruthie "Billie Idol" Weiss.

Like many second-time parents, we doted less. We did not love less, but we were clearly less excited. We were much more exhausted. We also paid a little less attention. Around the time Ruthie turned one month old, Palmer started to tell me about things she had noticed that seemed off. By that time, we had been married for four years and had been together for six. But we also had roles. I was the physician and the scientist, so I would be the one who managed the business of the family health. Having grown up with a very neurotic physician father, I reacted by learning to minimize and dismiss things with ease. I was a minimalist, at least when it came to my health or the health of my family.

I will never forget where I sat in our kitchen that fall when Palmer came back from a playdate she had attended with a group of her friends and their new babies. She wasn't overly concerned, and sometimes I expected that she just wanted me to reassure her. She said she really did think there might be something wrong with Ruthie. In retrospect I now know that she was not looking for reassurance. She said Ruthie's eyes did not track, and she said she really noticed it when she picked up her friend Katherine's baby, who locked eyes with her as they smiled together.

I flat out dismissed it. I said something about how normal development is a spectrum and that Ruthie was just going to take her time doing things her way. Young parents all too often fall into the trap of comparing their children to other children. It almost never ends well.

A few weeks later, I got sick and decided to stay home from work. It was unusual but also probably not surprising, given that we had two kids at home under three. I distinctly remember that it was a Friday and that I looked forward to hanging out with Ruthie—alone. We did what sick adults and young babies do for most of the day: we slept. Sometime that afternoon I mustered the energy to change her diaper. I put Ruthie on her back, and as I got everything together, I noticed the slow rhythmic beating of her eyes back and forth like a metronome. It was mesmerizing. But then my mind raced. I recall having such uncontrolled thoughts a few other times in my life; my second year of medical school was relatively full of them. As I hovered over my daughter, it took but a few seconds to come to grips with the complete realization that something was indeed very abnormal.

In my stupor, I think I left Ruthie on her back on our bed and went to the room that then served as our study. I sat at the computer, opened the internet browser, navigated to UptoDate.com, and typed in "infant nystagmus." I clicked on the article, and what came back was a list of mostly horrible neurological conditions. Nowhere in the article did I see the word *normal*. But then it hit. My eyes fixated on it: "oculocutaneous albinism." And right then, I knew. I knew that the funny jokes about Billy Idol were not so funny.

I spent a few minutes convincing myself that I was wrong, but that was impossible. I went back to Ruthie, who incidentally smiled the entire time I was gone and practically has not stopped smiling since. I think I finally did change her diaper, and then I held her as I thought about how I would tell my wife Palmer when she got home from work later that day.

Of course, knowing that it was a Friday afternoon, I also knew that there was little chance we would get confirmation of the diagnosis until Monday at the earliest. I knew the weekend was going to be long. When Palmer finally came home, I asked her to sit down. That is a terrible thing to do, and I have never done it since: there is likely no more panic-inducing request in the English language. Palmer did not sit down, but instead started crying. She demanded immediately to know "What?" Mothers really do always know.

My mind was hazy, and even under the best circumstances I would have struggled. Maybe it was easier this way. Maybe being sick disinhibited me? So I told her, "I think I know what is wrong with Ruthie."

"What!!"

I said, "I think she has albinism."

Palmer immediately burst into tears. So did I. Her mind raced with images of evil characters from movies. Albino. Albino. That word. Our housekeeper came into our bedroom to check on us. She spoke almost no English but she did not need to.

We spent most of the next 48 hours crying. We were terrified. We were sad. We were angry. We managed to schedule an emergency visit to a great pediatric ophthalmologist for Monday afternoon and we waited. But we knew.

It took Dr. Day about one minute to look at Ruthie and to confirm that she had albinism. She didn't even have to look in her eyes, but she did. And she looked at us and said very directly, "Ruthie has albinism."

Our questions were mostly directed at how bad Dr. Day expected her vision to be, and with great prescience, she said she thought that Ruthie had some pigment and predicted her visual acuity would be about 20/200: what we could see from 200 feet, Ruthie would need to be 20 feet away from. Would she drive a car? Would she date? Could she go to a normal school?

Over the next few weeks, we experienced every emotion there was. Dr. Day arranged for us to talk to one of her former patients with albinism and her mother. The former patient's father, also an ophthalmologist, had diagnosed her albinism at birth. We went off to see a dermatologist. We went to the geneticist where we agreed we would do genetic testing on Ruthie. One of the darkest moments was the day we took her to have her blood drawn for genetic testing. I'm pretty sure it was the first time she had really cried.

The decision to do genetic testing was reflexive. We didn't think hard about why we should or shouldn't do it. We didn't think about how the information might change our thinking or Ruthie's management. At that time, we did not

consider that we very well might have learned the genetic basis for her albinism long before Ruthie was born or even while Palmer was pregnant. We did not think of the implications such knowledge might have had, especially at a time when we were unprepared to even know what it all meant. Of course this has had a great impact on me as a person and as a doctor. I do not now encourage my patients to do genetic testing reflexively, or just because they can. I encourage them to think hard about what the outcomes might be, what they might mean, how they might change things in a good way and a bad way. I encourage them to imagine how the results might impact them. How might it change their lives or their children's lives? What are the potential positive outcomes? What are the risks? I also remind them that we often cannot know in advance. Overall, I am a different person now. I am a different doctor now.

We also made time to see a therapist to discuss how we would communicate Ruthie's condition to her older sister, to our family, to our friends, and to the world. We even talked about whether we needed to tell anyone about her albinism. The discussion with the therapist was important and empowering. We knew how we would handle these questions, but it was important to say them out loud and to have the process validated. In retrospect, it was a very fast and very easy conversation, and we ended up spending the bulk of the hour talking about the challenges of parenting our genetically normal three-year-old.

Later that fall, we got her genetic testing back. It turned out that Ruthie had inherited one mutated copy of the OCA2 gene from me and one from Palmer. She was what is called a compound heterozygote and was left with two very partially functioning copies of the gene, and hence with albinism.

We eventually decided to tell everyone about Ruthie and her albinism. Palmer and I were very much aligned that we would not run from the reality. We would embrace it and we would share it. We wanted her difference to be as normal as it could be, and we knew we had to lead by example. We had to help the world be comfortable with Ruthie. Sharing the genetic responsibility may have made that easier. Since we knew that she had inherited a mutant copy of the gene from both of us, we also knew that we each bore 50% of the "responsibility." It made what was already a powerful partnership that much more of a real partnership. It was truly both of us. We grew comfortable with what lay ahead, and we grew comfortable discussing it.

Early on, I had thought about changing the direction of my brand-new lab to go after albinism. I think it's a common reaction among scientist parents. But I quickly convinced myself that I knew nothing about the eye; moreover, as I learned more about the pathophysiology, I convinced myself that there was little that could be done after the point that the retina had not developed normally. Furthermore, there was not at that time an easy path to editing Ruthie's genome. I did imagine that genetic engineering could someday help kids who were diagnosed right after birth. It always seemed that the eye would be a great place to

experiment with genetic engineering. But I focused instead on just loving and supporting the child I had, and not the one I wished I had.

Over the next few years, our initial fears and regrets morphed slowly into acceptance and then a full embracing of Ruthie with albinism. Sure, we had concerns. Top of the list was a worry that she would always be different. She would always be an outsider. These concerns were based in both the physical (she might not be able to play sports with her friends, she would look different) and the emotional (she might not have friends, she might not feel like she belongs, she might get teased). Ultimately, we realized how lucky she was—and really how lucky we were. All parents think their kids are special, but we knew this one was particularly special. Sure, she'd run into windows, and she had enough bruises and bumps to warrant a call to child protective services. It was annoying to her and to us to remember her hat and sunglasses. And sunscreen application was always a challenge. But these were exceptions. Overall, life with Ruthie was joy. It was pure joy.

We began to learn about how the world saw differences. We started to think about how we saw differences. The local science museum had obtained an alligator they named, "Claude the Albino Alligator." I remember when Ruthie's preschool planned a field trip there that Palmer was sure to remind the teachers that this was a potentially awkward moment. It went fine. Later, the museum ran a series of radio ads talking about why Claude lost his color. They were insensitive and in poor taste, and of course we never would have noticed if we did not have a child with albinism. Palmer eventually convinced me that we needed to do something, so I wrote a letter to the UCSF Chancellor at that time, Sue Desmond-Hellman, who was on the board of the museum, asking her to ask them to take the ad down. They did.

As Ruthie got older, chaperoning field trips became one of my favorite activities, and it was not for the obvious reasons. You see, on field trips, I got to see what would happen when Ruthie moved to the front to see a demonstration or a piece of art. Without fail, this would elicit a chorus of protests from the students who naively assumed Ruthie was just being pushy. And like clockwork, her classmates would immediately scold the other children in what became a regular act of spontaneous and beautiful advocacy.

The theme here is that despite deriving from a stable germ-line mutation, Ruthie's albinism had evolved from a disability we all wish she never had to something we learned to accept to something we celebrated to something we cherished. The practical reality is that we briefly considered having a third child. This led to a series of what if conversations over whether we would want to have another kid with albinism. Would it be helpful to Ruthie to have a sibling to share this with her? Would it serve to normalize her even more? Or was it unfair to that child, just as being legally blind was unfair to Ruthie?

In the end, we decided we would not have another kid, but we had decided that were we to change our minds, we would not do pre-implantation genetic screening, something that was readily available at that time. We would roll the genetic dice.

In my work in the lab, I spent most of my time with genetically modified mice. I knew that modifying the genome of a human would be possible, someday. I knew that modifying human germ cells would be possible. But I did not really think of using genetic engineering to treat or prevent albinism until November 2015, when I read a Tweet from a scientist I did not know but respected a lot: "Prediction: my grandchildren will be embryo-screened, germline-edited. Won't 'change what it means to be human.' It'll be like vaccination."

I read it a few times and then decided to respond: "Brings up so many hard questions. My daughter has OCA2. We did not have more kids but would not have screened. . . . But when she asks if she can see like the rest of us and just wants to read a book, I wonder if we are stupid."

This set off a long series of conversations with my friends, my family, my colleagues, with the world, and importantly with Ruthie. These conversations continue today and will continue for the rest of time. And while details change, the thread remains the same. We have been blessed to have Ruthie in our lives, and we have been especially blessed to have Ruthie with albinism in our lives. Ruthie, now 13, is very proud of who she is, and at least for now feels strongly that she is who she is because of her albinism and perhaps despite it. And while she still complains about her hat and sunglasses and sunscreen, and while it's obvious she thinks hard while watching her 16-year-old sister learn to drive, she remains steadfast in her commitment to loving herself as she is and seeing herself and her albinism as one. It is clear to us that Ruthie is special, and that not all kids with genetic disorders will ski or surf or play on an AAU basketball team. Nor will all kids have the rich life she does, supported by an amazing community of friends and family. Some kids won't walk. Some kids will die. But in the end, what we have learned at this point in our journey above any other point is that one can't know what it's like to parent a child with a disability until one knows. And without knowing, it is practically impossible to make an informed decision about whether and how to intervene.

This conversation has great weight in our family, in that we know beyond a doubt that had we known of Ruthie's condition before she was born, she would not be here today. She would have been filtered out as an embryo, or she would have been terminated. In the future, she might have been edited—perfected—fixed.

This is the crux of the conversation about the role of technology in medicine. Before this, I probably did not consider strongly enough the distinction between choosing to intervene because we can versus because we should. That's it. We

have at our fingertips these incredibly powerful tools that will permit us to do things that were unimaginable even 20 years ago. We can now diagnose genetic conditions pre-pregnancy. We can select genetically "optimal" embryos. In the near future, we will be able to fix the broken ones.

But having Ruthie in our lives offers us a perspective that we never could have had before she was here. We firmly believe that Ruthie's presence in this world makes it a better, kinder, more considerate, more patient, and more humane place. It is not hard, then, to see that these new technologies bring risk that the world will be less kind, less compassionate, less patient, when or if there are no more children like Ruthie. And of course the kids who inevitably end up here will be even less "normal" than they are today. The rest of the world will have an even harder time understanding and appreciating what they bring. And what is most disturbing to me is that I know that even as a highly educated person in this field, I would have chosen to use the technology to remove or fix Ruthie if I had had the chance. Maybe that is a function of our training as doctors and scientists that we strive to fix broken things. Or maybe it is a function of our culture of perfection. I can't say. But what I can say is that I realize that life is one gigantic series of random, stochastic events, and that the lottery that ended up with all of us here today involved chance and luck the magnitude of which we can barely conceive. We consider ourselves to have won this game. We are better as parents, better as people, and better as a family to have had this experience of learning from Ruthie. We believe the world is a better place for having kids like Ruthie in it, and we want the world to think hard about whether it really wants to go down a path of engineering a world where there are no Ruthies.