RRPF

RECURRENT RESPIRATORY
PAPILLOMATOSIS FOUNDATION

RECURRENT RESPIRATORY PAPILLOMATOSIS
PATIENT-LED FDA LISTENING SESSION

OCTOBER 27, 2022

SUMMARY

Disclaimer

Discussions in FDA Patient Listening Sessions are informal. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants. This report reflects the Recurrent Respiratory Papillomatosis Foundation's account of the perspectives of patients and caregivers who participated in the Patient Listening Session with the FDA. To the extent possible, the terms used in this summary to describe specific manifestations of Recurrent Respiratory Papillomatosis, health effects and impacts, and treatment experiences, reflect those of the participants. This report is not meant to be representative of the views and experiences of the entire Recurrent Respiratory Papillomatosis patient population or any specific group of individuals or entities. There may be experiences that are not mentioned in this report.

CONTENTS

SESSION OBJECTIVE 4
SALIENT POINTS FROM THE SPEAKERS IN THE SESSION 4
RECURRENT RESPIRATORY PAPILLOMATOSIS OVERVIEW 5
IMPACT OF RECURRENT RESPIRATORY PAPILLOMATOSIS 6
PARTNER ORGANIZATION 7
ATTENDEES 7
FDA DIVISIONS REPRESENTED 8
PATIENT AND CAREGIVER PERSPECTIVES 10
- CAREGIVER PERSPECTIVE ON LACK OF STANDARD OF CARE FOR PATIENTS WITH RRP 10
- PARENT’S DESIRE FOR A DIFFERENT TREATMENT APPROACH FOR RRP 11
- IMPACT OF RRP ON SOCIAL AND EMOTIONAL HEALTH 11
- NAVIGATING CARE OF A SPOUSE WITH MALIGNANT CONVERSION OF RRP 12
- TRAUMA AND THE MENTAL HEALTH TOLL OF RRP ON PATIENTS AND FAMILIES 14
- ACCESS BARRIERS TO TREATMENT OPTIONS AND EXPERT CARE 15
- A PATIENT’S JOURNEY WITH RRP (1971-2022) 16

QUESTIONS AND ANSWERS FROM THE SESSION 19
FINANCIAL DISCLOSURES 20
REFERENCES 21

SESSION OBJECTIVE

The objective of the session was to provide FDA staff with the patient and caregiver perspective on living with recurrent respiratory papillomatosis (RRP). As we approach a major paradigm shift in managing this disease from repeated surgical intervention to medical and systemic therapies, it is important to highlight the outcomes that matter most to patients and caregivers in the RRP community.

From Kim McClellan, RRPF President: *“It is my hope that today’s listening session will assist the FDA in making those decisions that impact our community. The patient voice has been missing and to see our voice now being part of what drives progress is more than we could have dreamed of just a few short years ago.”*

SALIENT POINTS FROM THE SPEAKERS IN THE SESSION

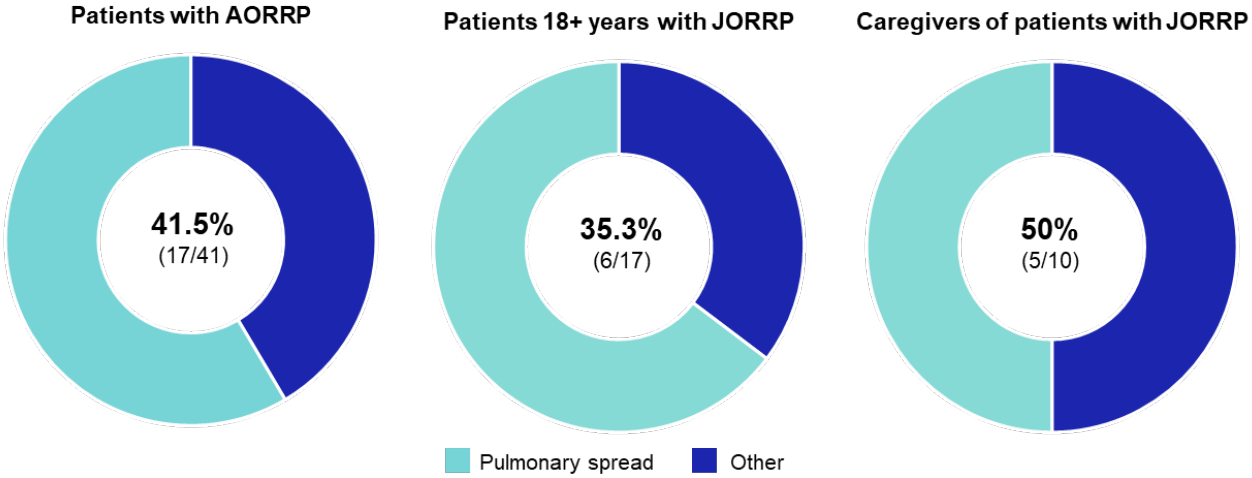
- The clinical manifestation of recurrent respiratory papillomatosis (RRP) in patients is heterogenous; making it difficult to understand the natural history of the disease, predict recurrence, and effectively manage
- Current standard of care for RRP is surgical management, which irreversibly destroys the laryngeal anatomy, causing much of the morbidity associated with the disease
- RRP exacts a heavy social, mental, and emotional toll on patients and their families. Patients’ inability to use their speaking voice and constant interruptions to daily life caused by repeated surgical interventions contributes to this toll
- Patients and families are desperate for non-surgical treatments for RRP, indicating that an end to surgery would mean “everything.” As a result, patients with RRP and their caregivers have a significant risk tolerance for new therapies. Many have indicated that any decrease in the number of surgeries would be worth the possible risk of side effects
- Disparities exist in the ability of patients to access non-surgical therapies
- Care for patients with pulmonary RRP requires a multidisciplinary team of specialists
- Routine screening for pulmonary RRP is currently not standard of care, despite evidence indicating a 32-fold increase in the risk for malignancy as compared with laryngeal RRP
- Because of the viral etiology of RRP, current clinical research for the treatment of RRP largely stems from the oncology field rather than the respiratory field, with therapies including immune checkpoint inhibitors and therapeutic vaccines
- Given that RRP is a rare disease with a heterogeneous presentation, and the current standard of care is surgery leading to an accumulation of scarring and damage to the anatomy, randomized placebo-controlled trial design(s) are not ideal and therefore should be carefully considered
- Any reduction in the number of surgeries is a meaningful outcome for patients and caregivers

RECURRENT RESPIRATORY PAPILLOMATOSIS OVERVIEW

RRP is a rare chronic disease caused by infection of the respiratory epithelium by human papillomavirus (HPV) types 6 and 11. Though not fully elucidated, the estimated incidences in children and adults in the United States are 4.3 and 1.8 per 100,000, respectively (Derkey 1995; Armstrong 1999). The infection causes the formation of squamous papillomas—or tumors—in the larynx. The age of onset for RRP displays a trimodal disease distribution and is traditionally designated as either juvenile-onset RRP (JORRP) or adult-onset RRP (AORRP) (San Giorgi 2016). This designation is based on age of symptom onset. JORRP is acquired from maternal/fetal transmission during childbirth. AORRP is acquired through sexual activity. JORRP is considered the more aggressive condition and is also more common (Omland 2014). Patients with RRP can develop malignancy, pneumonia, and acute respiratory distress requiring tracheostomy (Derkay 2008). The variability in the natural history of RRP contributes to the challenges related to its management.

The current standard of care is repeated debulking surgeries to remove the papillomas and relieve dysphonia and airway patency (Derkay 2008). Subsequent reactivation of latent HPV virus in remaining or adjacent tissues leads to papilloma recurrence. Patients can undergo hundreds of surgeries throughout their lifetime. These repeated surgeries, regardless of skillful execution, inevitably destroy the anatomy of the underlying larynx (Scatolini 2020). Paradoxically, the treatment for this disease is also the source of its morbidity. Pulmonary progression occurs in up to approximately 9% of patients with RRP (Pai 2022). There is a 32-fold increase in malignancy risk for patients with pulmonary RRP compared to patients with laryngeal RRP (Pai 2022). Pulmonary progression is one of the biggest fears of patients and caregivers (Figure 1).

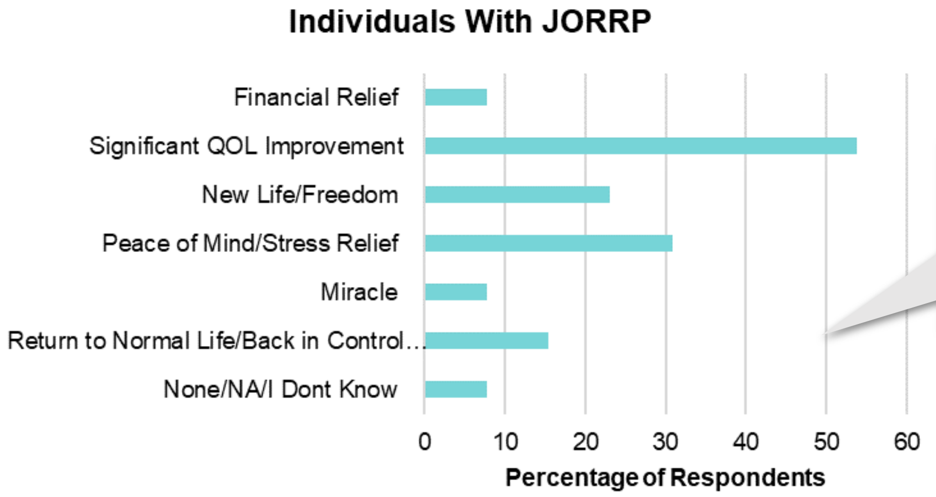
Figure 1. WHAT IS YOUR BIGGEST FEAR ABOUT YOUR RRP? *Data from the RRP Patient and Caregiver Experience Qualitative Survey. Participants included individuals with JORRP (18+ years) (N=13), Caregivers of children with JORRP (Under 18 years) (N=10), and individuals with AORRP (N=38).*



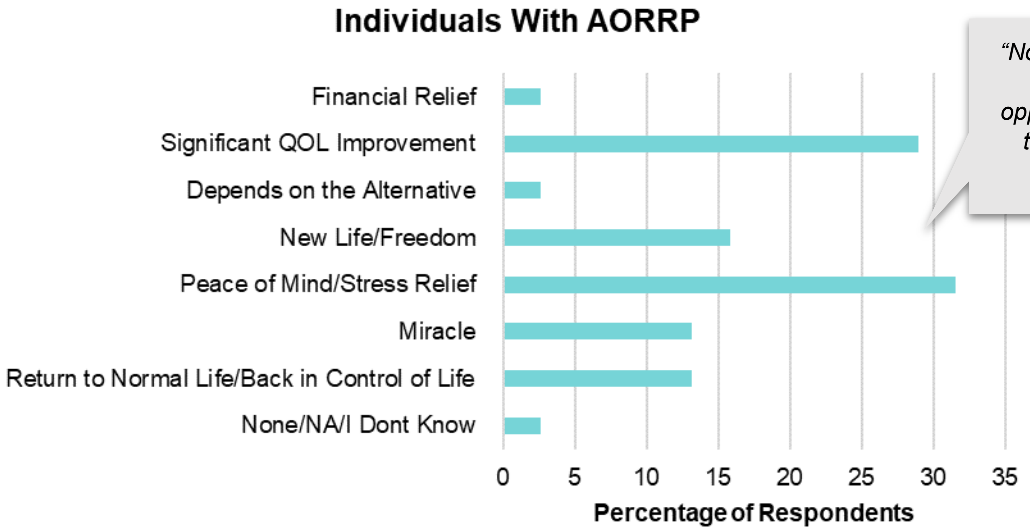
IMPACT OF RECURRENT RESPIRATORY PAPILLOMATOSIS

RRP not only impacts patients physically, but the disease wreaks havoc on the mental and social well-being of patients and families. The impact of RRP is multidimensional, and each of these aspects should be considered when examining the outcomes that matter most to this community. The RRPF conducted a qualitative patient and caregiver survey to better understand and capture the individualized burden that RRP placed on their lives. When patients and caregivers were asked what an end to surgical treatment would mean to them, the dimensions of impact were clear (Figure 2). It is clear that any reduction in the number of surgeries would be impactful to the lives of patients with RRP.

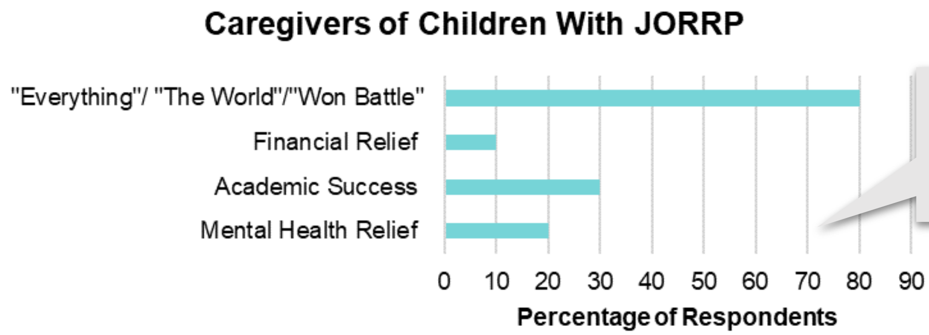
Figure 2. WHAT WOULD AN END TO SURGICAL TREATMENT OF YOUR RRP MEAN TO YOU? *Data from the RRP Patient and Caregiver Experience Qualitative Survey. Participants included individuals with JORRP (18+ years) (N=13), Caregivers of children with JORRP (Under 18 years) (N=10), and individuals with AORRP (N=38). AORRP, adult-onset RRP; JORRP, juvenile-onset RRP.*



"Zero surgeries would be the only improvement…Remission would be the only answer" –Adult with JORRP



"Not having to constantly think if I'll be able to have certain opportunities because of having to take 5 days of vocal rest" –Individual with AORRP



"Everything. Surgery is becoming more traumatic each time"
–Caregiver for a child with JORRP

A person's voice is intricately linked to their ability to perform in school or at a job. Patients with RRP often have extended periods when they are unable to use their voice at all. A 2010 study of AORRP and JORRP patients indicated that the Voice Handicap Index (VHI) score was associated with an increased risk for depression and anxiety disorders (18% of patients who scored above the VHI cutoff point had increased risk) (van Nieuwenhuizen 2010). In addition to losing a key communication tool, patients often cannot participate in activities of daily living, including social activities, due to the frequent recurrent surgeries required to maintain airway patency. In addition, the trauma of repeated medical procedures can lead to long-term effects such as PTSD, anxiety, and depression (Hall 2013). A recent study examined quality-of-life data from an international RRP patient registry (32 patients with JORRP and 14 patients with AORRP) (So 2022). The data support a heavy financial, mental, and social burden of RRP.

PARTNER ORGANIZATION

Recurrent Respiratory Papillomatosis Foundation

ATTENDEES

Craig Mabie, Patient with AORRP

Kim McClellan, Patient with JORRP and RRPF President

Chris Neuberger, Patient with AORRP and RRPF Board member

Amy Tichgelaar Milne, Caregiver to a patient with JORRP and RRPF Patient Registry Support

Mark Peikin, Caregiver to a patient with JORRP

Marcelle Stiff, Caregiver to a patient with pulmonary RRP

Lisa Tansey, Caregiver to a patient with JORRP and RRPF Director of Donor Development

Geoffrey Young, Caregiver to a patient with JORRP and RRPF Volunteer

FDA DIVISIONS REPRESENTED

Office of the Commissioner (OC) – *5 offices*

- OC/OCPP/PAS – Office of Clinical Policy and Programs/Patient Affairs (organizer)
- OC/OCE – Oncology Center of Excellence
- OC/OCPP/OCP – Office of Clinical Policy and Programs/Office of Clinical Policy
- OC/OCPP/OOPD – Office of Clinical Policy and Programs/Office of Orphan Products Development
- OC/OWH – Office of Women's Health

Center for Biologics Evaluation and Research (CBER) – *3 offices/divisions*

- CBER/OCD – Office of the Center Director
- CBER/OTAT/DCEPT – Office of Tissues and Advanced Therapies/Division of Clinical Evaluation and Pharm/Tox
- CBER/OTAT/DCEPT/GMBII – Office of Tissues and Advanced Therapies/Division of Clinical Evaluation and Pharm/Tox/General Medicine Branch II

Center for Devices and Radiological Health (CDRH) – *4 offices/divisions*

- CDRH/OPEQ/OHTI/DHTIC – Office of Product Evaluation and Quality/Office of Health Technology I/Division of Health Technology I C
- CDRH/OPEQ/OHTIII – Office of Product Evaluation and Quality/Office of Health Technology III
- CDRH/OPEQ/OHTIII/DHTIIIB – Office of Product Evaluation and Quality/Office of Health Technology III/ Division of Health Technology III B
- CDRH/OPEQ/OHTIII/DHTIIIC – Office of Product Evaluation and Quality/Office of Health Technology III/ Division of Health Technology III C

Center for Drug Evaluation and Research (CDER) – *6 offices/divisions*

- CDER/OCD – Office of the Center Director
- CDER/OND/OID/DAV – Office of New Drugs/Office of Infectious Diseases/Division of Antivirals
- CDER/OND/OII/DPACC – Office of New Drugs/Office of Immunology and Inflammation/Division of Pulmonology, Allergy, and Critical Care

- CDER/OND/OOD/DOII – Office of New Drugs/Office of Oncologic Diseases/Division of Oncology 2
- CDER/OND/ORDPURM/DRDMG – Office of New Drugs/Office of Regulatory Operations/Division of Regulatory Operations for Immunology and Inflammation
- CDER/OTS/OB/DBI – Office of Translational Sciences/Office of Biostatistics/ Division of Biometrics I

PATIENT AND CAREGIVER PERSPECTIVES

Caregiver perspective on lack of standard of care for patients with RRP

Lisa Tansey, mother to Eden, a patient with JORRP

Lisa's daughter Eden was diagnosed at 18 months with RRP. Prior to diagnosis, Eden was meeting all her developmental milestones, but Lisa had noticed that her cry had always been soft. Like most caregivers to children with a rare disease, Lisa began scouring the internet and research for information about RRP. She quickly became aware that RRP was very much a life-threatening condition for her daughter, having read about children suffocating in their sleep or succumbing to lung cancer after converting to malignancy. Eden's first surgical interval was 4 months and was the longest she would experience for years. The surgical intervals for Eden got shorter after each surgery. Lisa continued to search for alternative treatments.

The toll of Eden's RRP on the entire family was enormous, having to juggle childcare for siblings, surgeon schedules, and pre-op clearance appointments. It was apparent that there was no real consensus or standard of care for patients living with RRP. Eden did not have access to some of the newer experimental treatments available, despite being at a top hospital. Lisa and her family sought care outside of their hometown, even relocating to Mexico City with 3 young children to participate in a therapeutic vaccine study.

Eden's clinicians continued to weigh treatment options as her airway began to shrink from the repetitive surgeries and resulting accumulation of scar tissue. The most promising option was to remove one of her ribs and graft it into her airway to force it to remain open. Again, there were no standard-of-care guidelines to help guide Eden's treatment. Through her contact with the RRP patient community, Lisa learned of a few patients across the country receiving infusions of an oncology drug and showing substantial improvements in surgical intervals. She located an ENT and oncologist willing to administer the experimental therapy to Eden. Eden has received 12 infusions thus far and they are helping. The treatment has given her a chance at normalcy. Despite the unknowns about how long her body will tolerate the drug, it is currently the last treatment option for Eden. For Eden's parents, the trauma of constant surgeries far outweighs the potential risk of this oncology drug. Anything that increases the interval between surgeries is nearly always worth the risk to them.

> **“** ***I came across a therapeutic vaccine study in Mexico City that offered some hope. After speaking to numerous US clinicians regarding this therapy, my husband and I made the decision that I would move to Mexico City with my 3 young children and parents, to offer Eden a chance at surgical reprieve. With that, I interrupted family life and moved to Mexico, a place where I knew no one and did not speak the language.*** **”**

Parent's desire for a different treatment approach for RRP

Mark Peikin, father to Benjamin, a patient with JORRP

Mark is father to Benjamin, a male patient with JORRP. Mark noticed that Benjamin's voice was horse when he was less than a year old. Upon consulting their pediatrician about the hoarseness, Benjamin's parents were told it was nothing to worry about. At age 2, Benjamin's speech was not developing normally, and it was still difficult to understand him at times. After scoring well on a performance test following 6 months of speech therapy, his parents knew that there must be something else wrong.

Benjamin's parents consulted a top-rated ENT who was unwilling to scope him to confirm suspected voice nodules because he was only 3 years old. Benjamin's ability to participate in everyday activities such as playing sports or even walking around a department store continued to decline because of the impact on his breathing. His diagnostic journey took him to Boston where he was finally diagnosed with RRP. He underwent dozens of surgeries between the ages of four and nine years. Any improvements in his voice following surgery were not long-lasting and became less recognizable with each subsequent surgery. Frequent travel to Boston for recurrent surgeries began to take a toll on Benjamin's academics and social development. He was often bullied by other children because of his voice.

Mark could not imagine that surgery was the only treatment for his son. He was concerned that with continued repetitive surgeries, Benjamin's voice would continue to decline because of scarring, there would be an increased risk of the papilloma spreading, and the social and emotional trauma would continue. When Benjamin was 10 years old, he began treatment with an off-label vascular endothelial growth factor (VEGF) receptor inhibitor. The treatment has completely changed his life. He has not required any surgeries since starting treatment over a year ago. The infusion process takes less than two hours, which is a vast improvement from surgery requiring anesthesia, a day in the hospital, and weeks of recovery and voice rest.

> “ ***We still could not imagine that surgery was the only option and our search for an appropriate treatment for Benjamin continued.*** ”

Impact of RRP on social and emotional health

Craig Mabie, patient with AORRP

Craig was diagnosed with RRP at the age of 29 years. Prior to his diagnosis, he was a vibrant young man with a promising career as a director of sales and marketing. The toll that the surgeries took on his voice left him unable to perform essential duties for his job, which he lost as a result. The ability to speak is fundamental to the human experience. It is central to

In a quality-of-life study from an international patient registry, 74% of patients reported feeling limited in their career options due to RRP (So 2022) professional health, financial success, and social life. All these aspects suffered tremendously in Craig's life due to the impact of surgery on his voice.

> ***“RRP has caused some very dark times in my life…RRP had ravaged me with continued surgeries and absolutely no hope for a treatment or a cure. I was an isolated, sick, gay man. I was depressed, full of anxiety, and suicidal.”***

The cycle of repetitive surgeries began to dominate Craig's life. The cycles entailed voice loss from tumor growth, insurance pre-authorization, surgery preparation, surgery, physical recovery, voice recovery, insurance billing, and negotiation and settlement efforts. Each of the 102 times the cycle occurred, his life has ground to a halt. Many procedures caused acute throat and neck pain, difficulty swallowing and eating, intense discomfort from air passing over the open lesions in the larynx, fogginess from prescription pain medications, and medication-associated constipation. He lost his connection to his community and felt more isolation at times than what the average gay man experiences in America.

Craig is currently participating in a clinical trial. Because of the dramatic effects of RRP on his life, he has always had an extremely high risk tolerance regarding experimental therapies. According to Craig, success for a new therapy would be defined as no more surgeries. Or at the least to no longer be subjected to the voice loss-surgery-recovery-billing cycle. Craig feels that success would be to even have a reliable speaking voice which would greatly impact personal relationships in his life and provide new opportunities in all aspects.

> ***“WITHDRAWAL is a word that captures what a lot of the day-to-day RRP people, events, activities; withdrawal from life due to the inability to communicate vocally as a result of RRP”***

Navigating care of a spouse with malignant conversion of RRP

Marcelle Stiff, caregiver to Keith, a patient with pulmonary RRP

Marcelle's husband Keith is a patient with pulmonary RRP that has transformed to malignancy. Pulmonary RRP is the complication most dreaded by many patients. Keith was a fit, active, athletic 31-year-old when he inexplicably began to struggle breathing while climbing a flight of stairs. He repeatedly visited his primary care provider and received several rounds of antibiotics before eventually being rushed to the hospital in an ambulance. On the way to the hospital, he stopped breathing and was intubated.

Once the lesion in his trachea was identified as RRP, Keith underwent debulking surgeries every 10-14 days. His doctors suspected that malignant transformation was likely given the rapid and aggressive tumor growth. As feared, during the fourth debulking surgery, Keith's doctor confirmed squamous cell carcinoma. After finally finding a doctor with adequate experience at Memorial Sloan Kettering Cancer Center, Keith underwent a tracheal resection. This entailed his chin to be stitched to his collarbone for 4 weeks while the trachea healed, which was a better option than the alterative requiring a medically induced coma with an open incision for a week. Unfortunately, a full body scan following the resection revealed pulmonary papillomas in each lobe of Keith's right lung. The wedge resection biopsy revealed that the lesions had arisen in the lung, not the trachea. While multiple lesions are often seen in patients with pulmonary disease, it may not necessarily indicate metastasis as lesions can form independently in various locations, as was the case here. Keith underwent 5 rounds of chemotherapy (standard-of-care treatment for squamous cell lung cancer) and had two additional tumors removed.

Four years later, a routine scan revealed a 7 cm papilloma in Keith's left lung. Prior to his last surgery in 2013, a series of doctors over a year and a half recommended that Keith undergo no more surgeries unless absolutely necessary. Desperate to find an alternative to surgery, Marcelle and Keith consulted with doctors all over the country at top-tier facilities and unsuccessfully tried to enroll in three different clinical trials. While Keith continued to work full time despite his shortness of breath between bronchoscopies with laser ablation, Marcelle spent her days calling every doctor and researcher in the country. Eventually, it became apparent that the only option was surgery or Keith would die. After a successful surgery with a difficult recovery, including the development of chronic pulmonary aspergillosis, a fungal infection in the lung.

Consultation with several patients within the RRP community revealed that in many cases, pulmonary RRP was accidentally discovered. Despite this, many clinicians do not conduct routine screening for pulmonary disease in their patients. A recent publication in *Lancet Respiratory Medicine* by Dr. Sara Pai and colleagues indicated there is a 32-times increased risk of malignancy for patients with pulmonary RRP (Pai 2022). Given this finding and accounts from several patients, Marcelle believes that pulmonary RRP should be considered a pre-malignancy, or at the very least, high-risk disease.

> **“** ***Between 1999–2013, Keith had tracheal papilloma with conversion to cancer, and at least five pulmonary papillomas with conversion to cancer. He has had a tracheal resection as mentioned, chemotherapy, three open thoracotomies—meaning fully open lung surgery on both sides—one video-assisted thoracotomy on the right lung with smaller incisions, radio frequency ablation—which is basically microwaving the tumor through a needle inserted into the lung through the back, and brachytherapy twice—which is internal beam radiation given through a probe inserted into the bronchial tubes through the nose—with a failed third attempt, in addition to multiple bronchoscopies and biopsies. His lower left and upper right lobes were removed, along with pieces of the right middle and lower lobes.*** **”**

Trauma and the mental health toll of RRP on patients and families

Amy Milne, mother to Denver, a patient with JORRP

Amy’s son Denver, now 17 years old, has undergone 45 surgeries. Amy first noticed that Denver’s cry was weak when he was 10 months old. After visits to several doctors, worsening symptoms (development of wheezing and stridor), and numerous emergency room visits, Denver remained undiagnosed. He was eventually seen by a top ENT specialist at Seattle Children’s Hospital. His airway was almost completely blocked, and he underwent emergency surgery to save his life. Three weeks after his first surgery, his airway was almost completely occluded again. Denver’s papillomas continued to recur, requiring him to return to surgery every two to eight weeks. Throughout the repeated cycle, he would lose his voice and his family would worry about cancer and scar tissue accumulating and causing permanent effects on his voice. The medical treatment was unpredictable, and life was difficult. The severity of Denver’s illness made it difficult for Amy to remain employed and find childcare. Each appointment and surgery required a minimum of four hours of driving and two ferry rides. Amy worries about the effects of the anesthesia on Denver’s nervous system at such a young age. The mental health toll on the entire family has been significant. Amy believes there is a strong need for interventions that limit surgeries for patients with RRP. As Denver’s airway grew with age, the intervals between surgeries became longer. However, the mental health effects from years of traumatic surgery remain prevalent in the lives of the entire family.

In a quality-of-life study from an international patient registry, 79.5% of patients reported experiencing social anxiety due to their RRP symptoms (So 2022)

> **“ *Aside from the physical impacts of RRP on Denver’s airway, the mental health toll we have collectively experienced has been overwhelming. Denver has been in counseling since he was 4. We started with play therapy a few times a week. He has done psychodynamic therapy, cognitive behavioral therapy, integrative therapy, and seen some type of counselor most weeks of his life. Having worked as an Emergency Room RN for many years, I have seen patterns with a lot of the chronic medical kids. They lose hope, they become suicidal, and self-harm dominates. They don’t want any more interventions, appointments, opinions, and they ‘just want to die.’ Denver is no stranger to these sentiments.* ”**

Access barriers to treatment options and expert care

Geoffrey Young, father to Joshua, a patient with JORRP

Geoff always noticed Joshua’s voice was a little gravelly, but no one thought it was anything to be concerned about. Everything changed when Joshua was four years old and on a ski trip with his family. During the trip, he went from talking to whispering. Because Geoff is a head and neck surgeon who deals with respiratory issues, he took immediate action. He was able to reach out to his colleagues and get Joshua scoped very quickly. Once scoped, the papillomas in his airway were visible. Geoff contacted a colleague and was able to expedite surgery for Joshua to remove the papillomas.

The local ENT recommended that Joshua receive the HPV vaccine around the time of his first surgery. Because he was only 5 years old at the time, and the vaccine is indicated for children beginning at age 9, no providers in the area would administer the vaccine to him. The only option was to send him directly post-anesthesia to the adolescent and children’s clinic. There were no changes in his voice following the first surgery. As a clinician scientist, Geoff knew what a lifetime of repetitive, damaging surgeries would mean and did not want that for his son. He began researching alternative medical therapies and found evidence of success with off-label use of a systemic VEGF receptor inhibitor. Geoff called all his physician friends and colleagues and was eventually linked with Dr Karen Zur at Children’s Hospital of Philadelphia.

> **“ *We need an arsenal to treat this disease. And it needs to go beyond just surgery. Surgery is trimming the grass. The grass always grows back. We would like to eradicate these tumors, eradicate the potential for them to turn into cancers. We would like to eradicate the constant damage that’s done by repetitive surgeries…We need to look at systemic therapies.* ”**

After scoping Joshua, Dr Zur agreed that systemic therapy would be the best therapeutic option for him. Upon consulting with his local clinicians, Geoff learned that although there was awareness of the therapy, accessing insurance coverage for the therapy was challenging. Geoff utilized his connections and contacted the infusionist at the cancer center where he worked. He worked with his insurance network and hospital system to fight every denial for coverage. Finally, Goeff contacted the corporate offices of his insurance company and argued that there was variability in whether insurance companies were covering the therapy, but the therapy would likely outweigh the cost of expensive, morbid, and repetitive surgeries. Eventually, this argument convinced the insurance company to provide coverage. Joshua now receives infusions every 16 weeks, has no side effects, and has a normal voice. He is living a relatively normal life. Geoff is a researcher and understands the difficulties of conducting randomized controlled clinical trials in rare diseases. He argues that the placebo option is associated with significant morbidity from surgical scarring and carries the possibility of airway obstruction and possibly death. For these reasons, he believes that placebo-controlled trials are not a tenable solution for this patient population.

> **“*We should be able to make these treatments available to everyone. Not just to those of us who are lucky enough to have privilege to know the right people or how to read the studies or how to find these treatments. They should be available for everyone.*”**

A patient’s journey with RRP (1971-2022)

Kim McClellan, a patient with JORRP

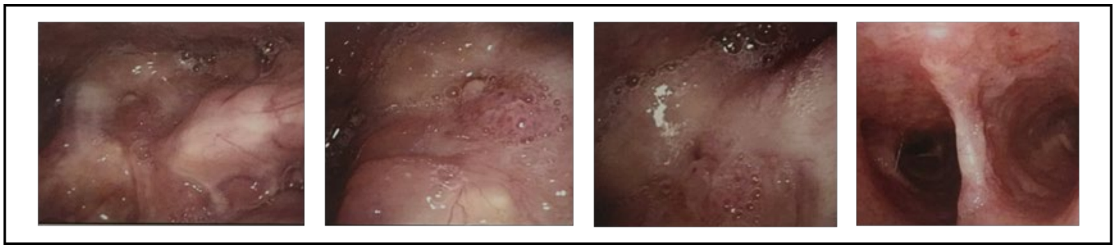
Kim was diagnosed at the age of 5 years and has lived with RRP for fifty-one years and endured more than 250 procedures. Despite living in a major city, her diagnosis was challenging and only came after a year of misdiagnoses. She admits to having gaps in her childhood memories, which she partially attributes to effects of repeated anesthesia on the developing brain, consistent with the literature (Bakri 2015). She recounts memories of her tongue being held with gauze during procedures, running away from nurses, and being teased by her peers. Patients with RRP often minimize the experience of living with years of repeated surgical intervention to cope with the associated mental trauma. This is also supported in the literature (Hall 2013). Each surgery means recovery from anesthesia, absences from school and work, returning to school or work with no ability to communicate for days, cost associated with expert care, and the constant worry about losing employment because of frequent absences.

In a quality-of-life study from an international patient registry, some patients reported paying more than 15% of their annual income toward RRP-related healthcare (So 2022)

> ***"Today, you are hearing the best voice I have had in over two decades. The voice that has waited so long to be heard. A voice I partly attribute to being able to afford to access expert care. We so often hear "hundreds of surgeries" and struggle to truly understand what that means to a patient. Today, I am sharing what even one less surgery in a calendar year would mean to the patient and their caregiver. One less surgery to watch your loved one, your child be taken away by an OR team. One less surgery to recover from the effects of anesthesia, which does take longer with age. One less surgery to get approval to miss work, miss school. One less surgery to return to work/school and be unable to communicate with those around you for days, sometimes longer. One less surgery to have a copay due, deductible payment due, as well as the cost associated with travel to expert care. Over 15% of RRP Registry patients report spending over 20% of their annual income on their RRP care/travel. One less surgery to cause worry of losing your employment due to absences. One less surgery to potentially cause pulmonary spread, which brings a 32 fold increase in malignancy risk compared to laryngeal RRP. Most importantly, one less surgery helps prevent my outcome from becoming their outcome-over 28 years with a tracheostomy because my airway is damaged from hundreds of surgical interventions leaving me with an airway of a small child, a life with pulmonary spread of the disease where malignancy is a daily concern, a life of medical trauma to not just myself, but to my entire family. Multiple all of this by 250 and you have my life with RRP, and the life of so many others. One less surgery matters."***

In 1991, after 250 interventions, the damage to the mucosal layer in Kim's airway became life-threatening. The laryngeal webbing and stenosis of the glottal area made debulking surgeries difficult to perform.

Figure 3. Endoscopic images of Kim's larynx after years of surgeries.



She underwent a tracheostomy which entailed an incision across her neck, insertion of a stent secured externally by two buttons, six weeks of recovery, and six weeks without the ability to speak. The first and second surgeries to place a stent were both unsuccessful. She had been decannulated from the second tracheostomy for less than a month when the stridor became worse, seemingly overnight. She recalls trying to communicate with her 5-year-old daughter about how to reach her father to get him to come home. Kim was in emergency surgery that evening. She awoke the next morning to discover that she had a tracheostomy and was told that she would never be decannulated. Her airway now required support. While her clinician viewed this procedure as lifesaving, Kim viewed this as life-ending. She would live the rest of her life with her tracheostomy in place. She was mentally defeated.

Since Kim's tracheostomy, she has had a pharyngeal tear from surgery, a mediastinal mass from that tear, a right thoracotomy to remove infection surrounding her lung, and has been diagnosed with pulmonary spread. She lives with the daily concern of airway obstruction and the increased risk of cancer associated with pulmonary disease. Four years ago, Kim was able to access an off-label systemic immunotherapy and begin treatment. She has only had one surgery in the four years since starting this treatment. She acknowledges that this may not be a long-term solution or a cure, but the therapy has offered her much needed reprieve from constant surgical intervention.

> “ ***For twenty years, everything about my RRP journey held true to the routine of surgery, recovery, airway compromise, surgery, recovery, airway compromise. As I sit here today, I realize that there's nothing routine about a lifetime of constant surgical interventions. Patients with RRP minimize the reality of frequent surgeries in an attempt to cope with the mental trauma they cause.*** ”

QUESTIONS AND ANSWERS FROM THE SESSION

Q: What would be a meaningful reduction in the number of surgeries, as it seems to vary widely?

A: There was a consensus from the patients and caregivers that any reduction in the number of surgeries would be impactful. Individual responses are summarized below.

Craig M: "No surgeries would be the win for me. I mean, just from the get-go. And if I had one less per year that would be a huge advantage, two less per year, an even bigger advantage. It's so omnipresent in my life that any reduction would be huge."

Kim M: "I have had over 250 surgeries. I quit counting years ago. These past few years where I have been able to do systemic therapy and not have to go to the OR has completely changed my life. To be able to make plans and know that I'm not going to have to cancel them because I'm going to need an emergency surgery. When I think about my journey with this disease and the repeated surgeries, lessening my surgical burden by even one less surgery per year would have brought my family, my parents, me, my friends such joy because one less surgery, means one less time that my parents would have had to kiss me on my forehead and say 'we'll see you in a bit' as I was wheeled away to surgery. One less surgery as an adult would be one less time I have to watch my spouse be strong for me when I know that tears are fixing to flow. So that when you think of surgery, this is not just a medical procedure, there is a mental component to it. Everyone on this call today, I'm sure you or someone you know very closely has had a surgery. So, take the worry you had for that person, multiply that dozens, hundreds of times over a lifetime. You will be able to easily see just one less procedure means a higher quality of life, impacts your economic burden for the disease. So yes, one less surgery matters."

Dr Simon B: "If I could just say as a surgeon here, the correct answer to this question is one. Right, there's no other correct answer. Any surgery to the vocal cords is traumatic, any surgery for papilloma carries with it the risk of a lifelong of permanent vocal damage. That was the point of what I was trying to say about the way that our vocal cords function and the way that they vibrate, the way that they produce sound, is completely irreplaceable. There's no other treatment option, there's no stem cell treatment that is going to recover vocal cord scar once it has occurred. So really any surgery they can avoid. One surgery over the course of someone's life is worth it because that reduces the risk of permanent vocal cord damage and that's a lesson that every surgeon who operates on vocal cords would confirm."

Geoffrey Y: "I wholeheartedly agree. I echo exactly what Simon has just said as a surgeon and as a parent. You know zero surgeries is my hope for my son."

Amy M: "I fear that one more surgery would create a situation where Denver attempts to end his life. The mental health burden has been unbearable."

Q: Would you please elaborate on the post-operative course and recovery time from surgery?

A: Patients and caregivers indicated challenges in recovering from anesthesia and other traumatic experiences. Individual responses are summarized below.

Kim M: "For me because I'm older, when I woke up from surgery it was taking longer to wake up. Instead of being awake almost immediately it can take 2 or 3 hours. Recovery at home, the anesthesia lingers longer the older you get, so I would have lingering nausea and other anesthesia impacts for days. It would typically be a full week before I felt like getting outside of my home again. For my voice, I was having surgeries so frequently my voice never recovered so it was always a strained whisper."

Lisa M: "There was a period of time where Eden was having surgery every 2 weeks. And by the time we got to that 4th round of every 2 weeks, the recovery was something that I could not have imagined. She was having so much difficulty clearing her airway that she would literally be coughing nonstop to the point where she was throwing up constantly because she could not stop gagging. She would be vomiting, she would be screaming, well screaming for her because her ears were hurting, her throat was hurting. There was nothing I could do. The doctors kept trying to give us medications that they thought would help but might have other side effects. It was just very dark to watch her, she was 4 at the time, watch her struggling and so confused as to why she was feeling this way. And as a parent, knowing that this was not the end. We were going to be facing more surgeries and more surgeries and I didn't know the best way to handle that. The post-op recovery is it varies every time. There's been times when she's been throwing up in the cab on the way home, just lethargic for days. It's different for everybody but the surgery is so traumatic, and the recovery is just as traumatic."

Amy M: "I also just want to remind everybody that recurrent general anesthesia and the post-op from coming out of general anesthesia is also incredibly difficult. Just the trauma of general anesthesia on these young brains. I think it's an area that hasn't been fully uncovered but as a mom, I see it."

FINANCIAL DISCLOSURES

None of the participants in the RRP Patient Listening Session received funding from the Recurrent Respiratory Papillomatosis Foundation for travel or participation. Additionally, the Recurrent Respiratory Papillomatosis Foundation did not receive any funding from any sponsor for participation in this Patient Listening Session.

Recurrent Respiratory Papillomatosis Foundation receives funding from a variety of sources, including sponsors. However, none of these funds were used for the purposes of organizing or participating in this Session. None of the participants in the meeting received compensation for attendance or participation.

Two participants in this Patient Listening Session have received support for research and consulting from a variety of sponsors:

- Dr Simon Best —Inovio Pharmaceuticals (Advisor)
- Kim McClellan – Teleflex (Advisor), Merck (Study Partner)

REFERENCES

Armstrong LR, Derkay CS, Reeves WC. Initial results from the national registry for juvenile-onset recurrent respiratory papillomatosis. RRP task force. *Arch Otolaryngol Head Neck Surg*.1999;125(7):743-748.

Bakri MH, Ismail EA, Ali MS, et al. Behavioral and emotional effects of repeated general anesthesia in young children. *Saudi J Anaesth*. 2015;9(2):161-6.

Derkay CS. Task force on recurrent respiratory papillomas. A preliminary report. *Arch Otolaryngol Head Neck Surg*.1995;121(12):1386-1391.

Derkay CS, Wiatrak B. Recurrent respiratory papillomatosis: a review. *Laryngoscope*. 2008;118(7):1236-1247.

Hall MF and Hall SE. When Treatment Becomes Trauma: Defining, Preventing, and Transforming Medical Trauma. *Ideas and Research You Can Use: VISTAS 2013.*Article 73.

Omland T, Akre H, Lie KA, et al. Risk factors for aggressive recurrent respiratory papillomatosis in adults and juveniles. *PLoS One*. 2014;9(11):e113584.

Pai SI, Wasserman I, Ji YD, et al. Pulmonary manifestations of chronic HPV infection in patients with recurrent respiratory papillomatosis. *Lancet Respir Med*. 2022;10(10):997-1008.

San Giorgi MR, van den Heuvel ER, Tjon Pian Gi RE, et al. Age of onset of recurrent respiratory papillomatosis: a distribution analysis. *Clin Otolaryngol*. 2016;41(5):448-453.

Scatolini ML, Labedz G, Cocciaglia A, et al. Laryngeal sequelae secondary to surgical treatment for recurrent respiratory papillomatosis in children. *Int J Pediatr Otorhinolaryngol*. 2020;130:109815.

So RJ, McClellan K, Best SR. Recurrent Respiratory Papillomatosis: Quality of Life Data from an International Patient Registry. *Laryngoscope*. 2022 Sep 30. doi: 10.1002/lary.30401.

van Nieuwenhuizen AJ, Rinkel RNPM, de Bree R, et al. Patient reported voice outcome in recurrent respiratory papillomatosis. *Laryngoscope*. 2010;120(1):188-92.