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ORIGINAL REPORT

Recurrent Respiratory Papillomatosis Foundation Position Statement on the Management of Adults With RRP

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ABSTRACT

Objective: With regulatory approval of HPV-specific immunotherapy for recurrent respiratory papillomatosis (RRP) and growing experience with systemic bevacizumab, a management algorithm incorporating these medical treatments is warranted.

Data Sources and Methods: RRP Foundation (RRPF) Key Opinion Leaders offer a proposed management algorithm for adults with RRP considering published literature and commercial drug availability.

Results: Preventative HPV vaccination should be considered for all patients. Determination of HPV type and pulmonary imaging are important for contemporary RRP patient care and assist in decision making. Risks and benefits of papilloma debulking as needed versus medical management of RRP must be deliberated on a patient case-by-case basis. HPV-specific immunotherapy that induces an HPV-specific T cell response to target the underlying HPV infection that is the cause of RRP is safe, offers the possibility of durable disease control following a short treatment course and is the recommended first-line medical treatment for patients who wish to avoid the risks of repeat procedural management. Papilloma disease control with systemic bevacizumab, which carries defined risks and must be continued for clinical benefit is the recommended second-line medical treatment for patients who do not achieve a complete response with immunotherapy and wish to continue medical management. For patients who elect to be treated with debulking procedures as needed, use of locally-administered adjuvant should be considered.

Conclusion: This proposed management algorithm from the RRPF serves as a contemporary resource and information guide for adult patients with RRP and their physicians considering treatment options.
Level of Evidence: 5

1 | Introduction

Both currently and historically, the mainstay of treatment for recurrent respiratory papillomatosis (RRP) has been surgical disease debulking. The discovery that RRP was caused by the low-risk HPV virus [1] and thus represents a chronic infection changed the understanding of the pathophysiology of RRP, but failed to change the treatment paradigm due to lack of safe and effective medical therapy. Although techniques used to control papillomatous disease have grown more elegant and precise over the decades, iatrogenic injury to sensitive laryngeal and tracheal tissue resulting in irreversible scar and laryngotracheal dysfunction remains a risk even under the care of the most experienced and skilled surgeons [2]. Additionally, repeat surgical and awake clinic-based interventions can exact an emotional, physical and financial toll on patients with RRP [3]. A cure for RRP implies total elimination of the causative infection, but would manifest pragmatically as a degree of disease control that allows RRP patients to avoid the need for repeat surgical procedures [3].

A lack of safe and consistently effective non-invasive treatment options has limited advances in standard of care management algorithms for RRP. With the Food and Drug Administration (FDA) approval of zopapogene imadenovec (Papzimeos, Precigen Inc.) [4], an HPV-specific immunotherapy designed to activate the immune system to detect and control or eliminate HPV-infected cells, and increasing evidence supporting systemic bevacizumab as an effective non-surgical approach to disease control [5], a new treatment algorithm for RRP incorporating these modalities is needed.

The RRP Foundation (RRPF; rrpf.org) offers a position statement outlining the diagnosis, workup and treatment of RRP in adults incorporating novel treatment advances as well as recommendations for HPV typing and imaging for pulmonary disease. The RRPF does not endorse specific drugs or provide medical advice but offers this position statement as a reference for clinicians caring for patients with RRP as well as an information guide for patients so that shared decision making can guide best practices. This manuscript was authored by RRPF-supported key opinion leaders (KOLs), with direct input from RRPF leadership (RRP patients and their caregivers) representing the voices of RRP patients.

Implementing patient-centered care with shared and informed decision-making between patients and their physicians requires consideration of all available treatments and their associated risks and benefits. The dominant theme of this manuscript is incorporation of newly available medical management options that could supplement or replace traditional papilloma debulking procedures. These medical treatment options should be offered to both patients with newly diagnosed papillomatosis and established RRP patients currently being managed procedurally. Historically, adjuvant medical treatment would be considered if repeated surgical interventions failed to adequately control the disease. The goal of early medical management is to address the causative infection at the time of diagnosis, and therefore to reduce or eliminate the need for repeated procedures prior to subsequent iatrogenic injury. In this new treatment paradigm, clinically indicated debulking procedures with or without the use of locally administered adjuvants would be reserved as a fallback treatment approach for patients who do not benefit from, do not tolerate, elect not to pursue after considering risks and benefits, or have no access to medical treatments for RRP.

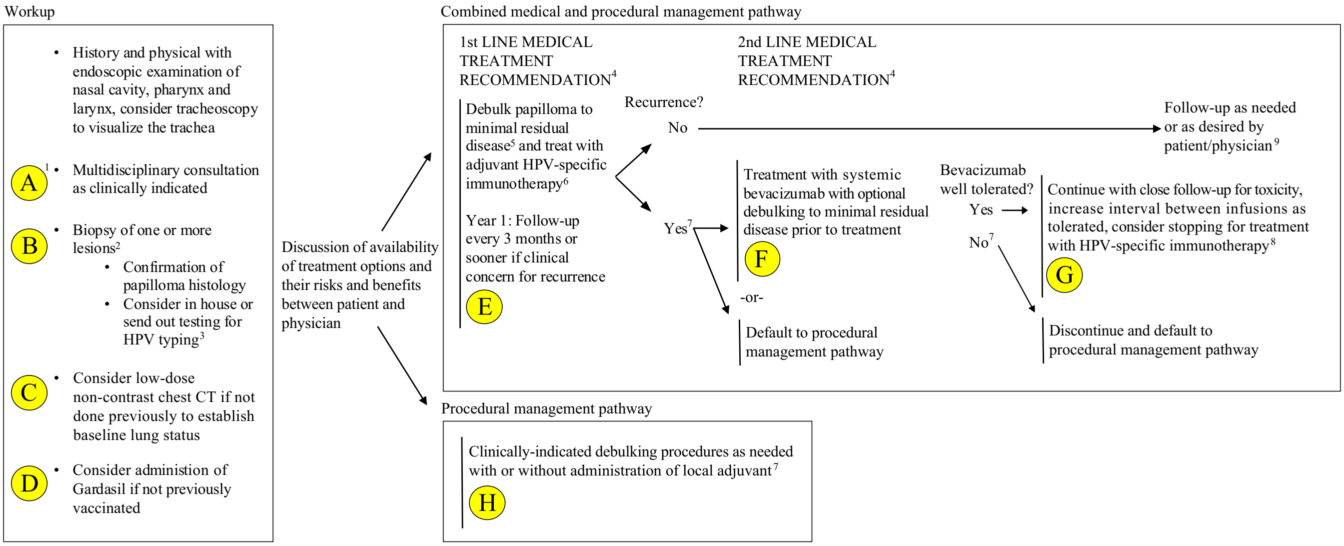
2 | Proposed Management Algorithm

Adopting the management algorithm style of the National Comprehensive Cancer Network (NCCN), our proposed management algorithm for adults with RRP using currently available commercial products is illustrated in Figure 1. For each algorithm decision branch highlighted with alphameric yellow circles, text discussion is included to provide the rationale for the recommendation.

2.1 | Recommendation to Consider Establishing a Multi-Disciplinary Team for the Care of Adults With RRP

As an initial general recommendation, the RRPF KOLs strongly recommend the implementation of a multi-disciplinary approach for the care of adults with RRP, led by an otolaryngologist. Early implementation of the first- and second-line treatments recommended below will likely require close multi-disciplinary collaboration among otolaryngologists, medical oncologists, and clinicians from other specialties. Medical treatment of RRP currently in use (systemic bevacizumab) is implemented through medical oncology, and early implementation of new medical treatments (HPV-specific immunotherapy) may be the same. Otolaryngologists will continue to serve as the primary clinician for adults with RRP, given their ability to diagnose the disease, to perform papilloma debulking to minimal residual disease, and to monitor with endoscopic exams throughout medical treatment. Whether in the operating room or the clinic, otolaryngologists will also continue to perform clinically indicated papilloma debulking procedures as needed for progressing disease that is refractory to medical management or for patients who elect to not pursue medical management. Finally, pursuant to the recommendations below, adult RRP patients identified to have pulmonary RRP will require input and expertise from additional specialists to properly manage these lesions.

As part of a multi-disciplinary approach, the RRPF KOLs recommend clear and routine documentation of clinical response to any treatment that, at a minimum, describes any change in



1 Yellow circles identify manuscript discussion points
2 If available, archived pathology specimens can be used for patients already diagnosed with RRP
3 Testing for HPV type at home pathology department or low-risk HPV send out test to Cincinnati Children's Hospital to distinguish between HPV6 or HPV11 positivity, if feasible
4 For patients with newly diagnosed RRP or patients already diagnosed with RRP and being treated with repeat clinically-indicated interventions.
5 Conservative debulking is recommended to reduce risk of scar formation
6 At the time of publication, zopapogene imadenovec (Papzimeos) is the only FDA-approved treatment for adults with RRP
7 Consideration of available clinical trials is recommended for all patients that fail first line or second line medical therapy or are managed with debulking procedures
8 Level 2 data indicates that systemic bevacizumab can be restarted with similar efficacy after stopping an initial treatment course if a complete response is not observed with HPV-specific immunotherapy
9 Consider low-dose non-contrast chest CT at least once every 5 years for patients with no lesions on initial screening CT, or annually for patients with known or suspected pulmonary RRP lesions to track radiographic changes

FIGURE 1 | Flow chart showing the proposed management algorithm for adults with RRP. Yellow circles identify manuscript discussion points.

the need and clinical indication for papilloma debulking procedures in patients with established RRP. The RRPF KOLs suggest that providers also consider the use of tools that objectively quantify change in disease burden, such as the Derkay score, and tools that subjectively quantify change in function, such as the VHI-10 questionnaire in patients whose disease manifests as dysphonia. Such documentation will assist in retrospective analyses of efficacy with real-world implementation of medical treatment for RRP.

2.2 | Recommendation to Perform HPV Typing on All RRP Patients

The RRPF KOLs recommend that HPV typing be performed on every adult RRP patient, as it is available at many centers and offers significant diagnostic, clinical, and research benefits. This test can be performed on either new or archived papilloma tissue. HPV typing helps reduce the chance of diagnostic error, as this test is sensitive and specific for RRP and helps rule out other pathologic mimics, including papillary-variant squamous cell dysplasia or carcinoma [6]. Research teams that have typed RRP clinical specimens with contemporary approaches find HPV 6 or 11 in most samples [4, 7]. Although differences exist in the sensitivity of different assays used to detect HPV, published reports indicate that some RRP patients can have disease positive for HPV subtypes other than 6 and 11, such as 16, 18, 31, 44, 45, 55, and 70 [8–10]. Additionally, most non-recurrent papillomas in the upper aerodigestive tract but outside the larynx are not positive for HPV [10], suggesting that solitary non-recurrent papillomas are a different disease entity and should not be classified as RRP. HPV-specific immunotherapies developed for the treatment of RRP are designed to induce HPV 6 or 11-specific T cell responses [4, 7], and no evidence exists as to the clinical benefit in patients whose papilloma is negative for these two HPV types. Testing for and documenting HPV positivity will allow real-world data to accumulate. Widespread availability of RNA in situ hybridization (RNA-ISH) to detect low-risk HPV in most pathology departments in the United States makes strain-selective HPV genotyping feasible for clinical screening, acknowledging that RNA-ISH is inconsistently available outside the United States. Typically, RNA-ISH provides a positive or negative result for low-risk HPV [6, 11] but does not specify the HPV type.

Arguably, additional clinical rationale exists for specific HPV typing to determine if an individual's papilloma is positive for HPV 6 versus 11. Some studies observe that HPV 11-positive disease is associated with a more aggressive clinical course compared to HPV 6-positive disease [9]. Specifically, patients with HPV 11-positive disease tend to have an earlier age at disease onset, require a higher frequency of clinically indicated interventions throughout their lifetime, have a higher risk of developing pulmonary lesions, and face a higher risk of progression to malignancy, including lung squamous cell carcinoma [8, 9, 11–13]. Thus, HPV 11 positivity predicts more aggressive disease, which may guide specific clinical evaluation or follow-up decision-making for clinicians. Further, with implementation of HPV-specific immunotherapy treatment, real-world data that allow tracking of responses to new therapies based upon HPV type will have value for providers as they counsel patients on the risks and benefits of its use. Finally, truly type-specific HPV immunotherapies, such as cell therapy, are the subject of ongoing investigation. Implementation of routine HPV typing for patients with RRP now will allow for easier implementation of these new treatments, if proven to be safe and effective. For clinicians with lack of access to pathology departments that offer type-specific HPV testing, we recommend the clinically validated Cincinnati Children's Hospital send-out test performed in a Clinical Laboratory Improvements Amendments (CLIA)-certified, College of American Pathologists (CAP)-accredited laboratory that uses droplet-digital polymerase chain reaction (PCR) to detect HPV 6 or 11 with high specificity. Information on this send-out low-risk HPV test can be found online [14].

2.3 | Recommendation to Obtain Low-Dose Non-Contrast Chest CTs to Screen for and Follow Pulmonary RRP

Pulmonary RRP lesions can manifest as cystic or solid masses in the lungs and are present in up to 8% of pediatric RRP patients [15, 16], but the prevalence of pulmonary RRP lesions in the adult population is unknown. Identification of pulmonary lesions in patients with RRP is associated with up to a 32-fold increased lifetime risk of malignant transformation into lung cancer compared to the overall RRP population [17, 18]. Thus, it is important to establish the prevalence of pulmonary disease in adult RRP patients and to identify patients with pulmonary lesions early to facilitate multidisciplinary discussion about a comprehensive surveillance and management plan. The multi-disciplinary team for pulmonary RRP patients should include clinicians familiar with the management of pulmonary RRP and its manifestations, and may include pulmonology, thoracic surgery, interventional radiology, interventional pulmonology, and pathology. RRPF KOLs agree with the recommendations set forth by the RRPF pulmonary RRP working group consensus statement and recommend that all adults with RRP consider having a low-dose non-contrast chest CT scan (LDCT) at the time of diagnosis or at the time of next follow-up in RRP patients who have not had a screening chest CT [19], acknowledging that this recommendation is based primarily on data from studies of pediatric RRP populations. Adult RRP patients who have an initial negative CT scan and do not meet criteria for annual lung cancer screening should consider having a new chest LDCT every 5 years [19]. RRPF KOLs feel that increased vigilance is warranted for patients with infraglottic disease but no evidence of pulmonary lesions on initial LDCT, and that more frequent screening for pulmonary lesions should be considered if a change in disease severity is observed in this population [17]. Adult RRP patients who meet criteria for annual lung cancer screening should continue with their annual LDCT according to that screening guideline. If a pulmonary lesion biopsy at any point reveals the presence of a cancer, the patient should be referred to a multi-disciplinary lung cancer team for expert management and follow-up.

2.4 | Recommendation to Administer Preventative Vaccination to All RRP Patients

Nonavalent HPV preventative vaccine (9vHPV, marketed as Gardasil-9 in the Unites States) is a preventative vaccine developed to prevent high- and low-risk HPV infection, which offers RRP patients protection against other HPV-subtypes, and there is some evidence it has therapeutic benefits for adults already diagnosed with RRP.

First and foremost, 9vHPV administration is safe, with little to no risk [20]. The US Centers for Disease Control and Prevention (CDC) maintains active surveillance of 9vHPV's adverse events through the Vaccine Safety Datalink (https://www.cdc.gov/vaccine-safety-systems/vsd/index.html) and the Vaccine Adverse Event Reporting System (https://vaers.hhs.gov/). The CDC consistently maintains that 9vHPV administration is of very low risk, with an overwhelming body of data supporting its favorable safety profile. Adverse effects reported in clinical trials were minor and consistent with product characteristics, such as pain at the injection site, fatigue, headache, malaise, and vomiting. The Advisory Committee on Immunized Practices (ACIP) reports no HPV vaccine-related deaths and fewer than 1% serious adverse events, similar to placebo [20]. This information is critical, as RRPF KOLs acknowledge the importance of providing education to and dialog with patients to reduce medical mistrust and diminish vaccine hesitancy.

Multiple retrospective case series suggest that adults of all ages with RRP may clinically benefit with lengthened intersurgery interval (ISI) and reduced recurrences following adjuvant 9vHPV administration [21]. A prospective single-arm clinical trial by Smahelova et al. involving 42 adult RRP patients (ages 21–73) reported a decrease in recurrences from 0.85 per year before vaccination to 0.36 per year after vaccination over a 5-year follow-up [22]. This study also highlighted that both newly-diagnosed RRP patients and those with highly recurrent disease showed equal benefit following HPV vaccination, suggesting that early administration also leads to clinical benefit. A meta-analysis by Goon et al. found an overall reduction of 0.123 recurrences or surgeries per month, again suggesting that HPV vaccine is a beneficial adjuvant treatment [23].

The underlying mechanism for the possible therapeutic effect of prophylactic HPV vaccines is not fully understood, but it is hypothesized that the induction of high serum levels of neutralizing antibodies may play a role. RRP patients develop at least 100-fold higher levels of HPV vaccine type-specific antibodies compared to before vaccination, and they remain significantly elevated (10 times higher than pre-vaccination levels) for at least five years [22]. This induction of a robust humoral immune response is thought to reduce potential mucosal reinfections at the papilloma site and possibly inhibit the reactivation of latent HPV in adjacent epithelium. Additionally, since the current formulation of 9vHPV is nonavalent, these high levels of HPV-specific antibodies will also provide the patient with protection against 8 other subtypes of HPV infection.

Despite limitations in existing studies, such as small sample sizes, retrospective designs, and lack of complete understanding of the mechanism, strong evidence of safety and consistent clinical benefit supports the use of 9vHPV in adult RRP patients. In agreement with the Triologic Society Best Practice report [24] and evidence supporting clinical benefit in all ages [25, 26], the RRPF KOLs recommend administration of 9vHPV in all adult RRP patients if not previously vaccinated. Otolaryngologists can refer patients to their primary care physician for 9vHPV administration or provide a prescription for 9vHPV to the patient directly.

2.5 | Recommendation for First-Line Treatment of Adults With RRP With HPV-Specific Immunotherapy

Treatment of adults with RRP should address the underlying chronic HPV infection that is the cause of this disease. Given that papillomas do not harbor driver mutations [27] and, to the best of our current knowledge, are caused purely by the chronic HPV infection, control or elimination of the viral infection should result in less or no papilloma recurrence and reduce or eliminate the need for surgical procedures that carry risk and do not cure disease. The ideal treatment would have an excellent safety profile, a short, defined course of treatment, and generate an HPV-specific T cell immune response that addresses the underlying chronic viral infection. HPV-specific immunotherapy designed to durably enhance HPV 6 and 11-specific immune responses has a demonstrated safety and efficacy profile and is the treatment modality that best matches this therapeutic aim.

In August 2025, the FDA granted Full Approval to zopapogene imadenovec for adults with RRP. This is the first-ever and currently the only approved treatment for RRP, and one that addresses the underlying chronic HPV 6 or 11 infection that is the root cause of most RRP. Zopapogene imadenovec is a non-replicating adenoviral vector-based immunotherapy designed to activate HPV 6- or 11-specific T cell responses to induce immune control or elimination of HPV-infected cells. The approval was based on safety and clinical benefit observed in an open label, single-arm phase 1/2 clinical trial in 35 adults with RRP conducted at the National Institutes of Health [4].

The foundation of any treatment recommendation, especially a first-line treatment, should be based on the risk vs. benefit profile. First and foremost, HPV-specific immunotherapy appears to be very safe. Patients who received the four-injection course of zopapogene imadenovec treatment experienced self-limiting injection site reactions (tenderness, swelling) and constitutional symptoms (low grade fever, body aches, chills) for 24–48 h, very similar to symptoms that many individuals experience with systemic immune activation after common preventative vaccines [4, 28]. Importantly, serious treatment-related adverse events, such as auto-immune side effects, were not observed. Per the clinical trial design and FDA-approved label, zopapogene imadenovec is administered as an adjuvant over a 12-week period after an initial papilloma debulking procedure, repeated as needed prior to the 3rd and/or 4th administration, that reduces the papilloma to minimal residual disease in order to reduce the immunosuppressive papilloma microenvironment [28, 29] and allow the enhanced immune response in circulation from the immunotherapy to have maximal local effect. Half (51%) of patients experienced a complete response, defined by the trial as no need for any clinically-indicated interventions in the 12 months after the immunotherapy. Patients in this trial required, on average, over 4 interventions (range 3 to 10) in the year prior to receiving treatment. The disease control was durable, with 83% of the complete responders still not requiring an intervention with a median follow-up time of over 3 years after treatment [30]. Most of the patients who did not achieve a complete response still required fewer clinically-indicated interventions after treatment. Overall, 87% of adult RRP patients who received treatment required fewer interventions after treatment compared to before. Voice handicap (measured by VHI-10) was significantly improved, even in those who had required a large number of procedures prior to treatment [31]. Removal of papilloma that was residual after or had progressed since the initial papilloma debulking was performed prior to the 3rd and/or 4th administration of zopapogene imadenovec in most patients. Whether the 14 of 18 patients who achieved a complete response and underwent one or two on-treatment procedures would have still achieved a complete response without these additional debulking procedures to remove the immunosuppressive papilloma microenvironment is unknown. Accumulation of real-world data on patients and their providers who elect to not perform additional debulking procedures despite the presence of residual or progressed papilloma while receiving zopapogene imadenovec will be informative.

HPV-specific immunotherapy therefore offers a combination of safety and efficacy, along with a mechanism of action that addresses the chronic infection, such that RRPF KOLs strongly recommend that all adult patients with RRP be offered a course as early as possible when recurrent disease is detected (first-line treatment). This approach offers adults with RRP the best chance of safely gaining durable disease control while avoiding additional debulking procedures following a one-time short, defined treatment course. We do not recommend withholding the option of HPV-specific immunotherapy based on surgical or procedural thresholds. As patients and physicians discuss the risks and benefits of HPV-specific immunotherapy, factors such as each patient's historical procedural frequency will likely influence treatment decision making, and patients that require infrequent debulking procedures may elect not to proceed with medical management. However, the RRPF KOLs feel that the option of HPV-specific immunotherapy should not be withheld based upon physician perception of a patient's disease severity. RRP patients should be empowered to make their own treatment decisions after considering the risks and benefits of both medical and procedural management.

Early implementation of HPV-specific immunotherapy may require the multidisciplinary approach advocated for in Recommendation A and involve medical oncology. Administration of zopapogene imadenovec as a subcutaneous injection is straightforward, but it requires ultra-cold storage prior to administration that is unlikely to be present in otolaryngology clinics not embedded within academic medical centers. With real-world use experience, these therapies may transition away from medical oncology infusion centers and day hospitals and toward outpatient medical oncology or otolaryngology clinics. The more broadly available, the more this will reduce treatment barriers and ensure all adult patients with RRP have access to these new treatments.

2.6 | Recommendation for Second-Line Treatment of Adults With RRP With Systemic Bevacizumab

For patients who do not achieve a complete response without disease recurrence following treatment with HPV-specific immunotherapy, the risks and benefits of continued medical management will need to be considered. Some patients may elect to start or resume the use of clinically indicated debulking procedures to control their disease. For patients who wish to continue medical management aimed at eliminating or reducing the need for debulking procedures, off-label use of systemic bevacizumab offers adults with RRP the best chance to safely control or eliminate papillomatous disease burden. This in turn reduces or eliminates the need for debulking procedures, and therefore systemic bevacizumab should be considered the recommended second-line medical treatment. Historical procedural frequency, underlying medical conditions, and access to an infusion center are all important factors to be considered.

Clinical experience and evidence demonstrate that off-label use of systemic bevacizumab leads to an almost universal clinical response, effectively reducing or eliminating the need for debulking procedures [5, 32–34]. Bevacizumab works by targeting vascular endothelial growth factor (VEGF), which is highly expressed in RRP lesions, thereby disrupting existing tumor vasculature and preventing new vessel formation to reduce papilloma growth. Rapid and dramatic regression of papillomatous lesions can be observed with systemic treatment, including in patients with diffuse tracheal involvement for whom local treatments are impractical. Patients can achieve sustained clinical remission with continued bevacizumab, while infusion frequency can be gradually reduced in many patients, often up to 12-week intervals [5]. Furthermore, the treatment is generally well-tolerated, with well-established risks including renal impairment that can be followed with routine laboratory tests to allow dose reduction or withdrawal of treatment prior to irreversible damage. Additionally, multiple bevacizumab biosimilars are now available that are highly effective at papilloma disease control. Zirabev (bevacizumab-bvzr, Pfizer) treatment resulted in a 100% response rate with good treatment tolerability in a prospective clinical trial of adults with RRP at the National Institutes of Health [35]. This trial also demonstrated a 100% response rate to treatment in patients who had previously received HPV-specific immunotherapy and did not achieve a complete response. The RRPF KOLs support the use of systemic parent bevacizumab or bevacizumab biosimilars as a second-line medical management option.

Clinical experience also indicates that some RRP patients receiving systemic bevacizumab need to stop treatment due to denial of coverage or development of adverse events [34]. Others may choose to stop treatment due to the need for recurrent infusion center visits and blood work to monitor for treatment-related toxicity. The primary drawback of systemic bevacizumab treatment is that it must be continued for disease control. Withdrawal of treatment leads to near-universal disease recurrence because bevacizumab does not address the underlying HPV infection that is the cause of RRP [5, 34]. This leads to a clinical situation in which adults with RRP who achieve good control with systemic bevacizumab must continue treatment indefinitely or until toxicity becomes unacceptable. This is the primary reason that the RRPF KOLs recommend systemic bevacizumab as second-line, and not first-line, medical treatment to eliminate or reduce the need for debulking procedures.

2.7 | Recommendation That Adults With RRP Currently Controlled With Systemic Bevacizumab Should Attempt Durable Disease Control With HPV-Specific Immunotherapy

For those adults with RRP currently controlled with bevacizumab, cessation of their systemic infusions will lead to a near-universal recurrence of papilloma, indicating that the causative viral infection is still present [5, 35]. Therefore, the RRPF KOLs recommend that patients currently on systemic bevacizumab receive a full treatment course of HPV-specific immunotherapy, while the disease is in a minimal residual state, just as it would be following initial surgical debulking. Conceptually, systemic bevacizumab has accomplished what the surgical treatment could have accomplished in terms of reducing disease burden, but without the risk of surgery itself. Systemic bevacizumab should be stopped prior to initiating HPV-specific immunotherapy since no patients treated with the approved HPV-specific immunotherapy were on systemic bevacizumab at the time of enrollment [4], and the safety of combination treatment is currently unknown. Systemic bevacizumab can be resumed as soon as disease progression occurs following completion of HPV-specific immunotherapy if a durable response is not achieved. Systemic bevacizumab can safely be restarted after a treatment pause, with similar efficacy in controlling papillomatous disease [5, 35].

2.8 | Recommendation for Use of Locally Administered Adjuvant Therapy for Patients Who Elect Procedural Management of Their RRP

After discussing the risks and benefits of treatment options with their clinician, some patients may choose to have debulking procedures as needed to palliate their dysphonia or airway obstruction as either their primary treatment modality or, if newly diagnosed, for a period of time to establish the frequency of recurrence of their disease. Multiple factors may influence the decision to continue with debulking procedures as primary management, including an individual patient's historical frequency of clinically indicated procedures or concern about possible side effects from medical management. Certainly, some patients will not respond to or tolerate the available medical treatments and default to treatment with clinically indicated debulking procedures. Other patients may not be presented with the option to receive medical management, either due to physician preference based upon historical practice patterns or lack of institutional access to medical treatment options. For patients who are not offered systemic treatment, they will need to decide whether they desire to seek additional consultation.

For patients who decide to or must proceed with clinically-indicated debulking procedures as their primary treatment approach, the RRPF KOLs recommend consideration of the use of the locally-injected adjuvant bevacizumab. Similar to systemic administration, locally-administered bevacizumab inhibits blood vessel formation to reduce papilloma growth. When administered as an adjuvant with angiolytic laser ablation of focal papillomatous disease, local bevacizumab may safely contribute to control of papillomas [36, 37]. However, locally-injected bevacizumab is impractical to use for extensively multifocal disease, tracheal, or distal airway disease.

Cidofovir is another locally-injected adjuvant treatment for adults with RRP historically used by many clinicians. Cidofovir is a nucleoside analog that competitively and selectively inhibits viral DNA polymerase activity. HPV viruses do not encode a viral DNA polymerase and instead utilize the host (human) enzyme, indicating that cidofovir must be used at high concentrations to achieve an effect. Prospective clinical trials designed to study the efficacy of locally-injected cidofovir demonstrate either no significant difference between the placebo and cidofovir treatment groups or a reduction in disease burden (Derkay score) but no reduction in the need for clinically indicated debulking procedures [38, 39]. Studies comparing cidofovir to bevacizumab suggest a greater decrease in disease burden (Derkay score) and higher rate of complete response with cidofovir, but fail to show significant superiority of either in reducing the need for clinically indicated debulking procedures [39–41]. Early safety concerns about possible promotion of dysplasia within papillomas treated with cidofovir [42] led the manufacturer to discourage its off-label use. Although subsequent studies in primates and human subjects failed to show an increase in malignancy rates [43], the RRPF KOLs cannot formally recommend the use of cidofovir as an adjuvant treatment because of the manufacturer warning and posit that the use of cidofovir in adults with RRP should be the result of a risk/benefit discussion between the patient and physician.

2.9 | Recommendation to Consider Referral to a Clinical Trial for Adults With RRP Refractory to First- Or Second-Line Therapy or Those With Pulmonary RRP

Even with the success of first- and second-line therapies, there will still likely be some adult patients with RRP who require clinically-indicated surgical procedures to maintain acceptable vocal and airway function. Although patients can pursue a clinical trial at any point, patients who are refractory to first- or second-line medical management as outlined in this algorithm should be encouraged to pursue prospective clinical trials that explore alternative treatment strategies under controlled conditions. Although the RRPF KOLs feel that the medical management strategy outlined in this algorithm will allow most adults with RRP to avoid repeat debulking procedures, some patients may not tolerate or choose not to be treated with HPV-specific immunotherapy or systemic bevacizumab or may find these treatments financially prohibitive. Additionally, more research is needed to clinically develop effective treatment strategies for adults with pulmonary RRP. The medical management strategies recommended in this algorithm have not demonstrated the consistent ability to induce regression of pulmonary lesions [4, 33]. The effective treatment of pulmonary RRP remains a critical unmet need.

3 | Other Treatments Not Included in This Management Algorithm

Other treatment modalities have been studied in adults with RRP but are not currently included by the RRPF KOLs in the recommended management algorithm, either because they are not yet approved by the FDA or because they should not, in the opinion of the RRPF KOLs, be used outside of a clinical trial. These are summarized here.

1. A different HPV-specific immunotherapy from Inovio Pharmaceuticals called INO-3107 is also under FDA review. Although the technology used with INO-3107 is different from zopapogene imadenovec, the goal of enhancing HPV 6 and 11-specific immunity for the treatment of adults with RRP is the same. Open label, single-arm phase 1/2 clinical study of INO-3107 has also demonstrated evidence of clinical benefit in the majority of treated patients [7, 44, 45]. Further supporting evidence for the safety of DNA immunotherapy is the safety profile of INO-3107, with the most common side effects including injection site discomfort, fatigue, and headache, with no treatment-related adverse effects higher than Grade 2. INO-3107 is also used as an adjuvant treatment after surgical debulking, with a series of injections over 9 weeks. The majority (81%) of patients had a reduction in surgeries in the 12 months following the treatment, with durable responses showing a reduction in interventions at an average of 2.8 years following the trial [7, 44, 45]. If INO-3107 is granted FDA approval for adults with RRP, this RRPF-sponsored Position Statement management algorithm will be updated to include INO-3107 as another first-line immunotherapy treatment option.
2. Published or disclosed data from clinical trials using the immune checkpoint inhibitors (ICIs) avelumab, bintrafusp alfa, and pembrolizumab to treat adults with RRP are available [46–48]. In general, these studies demonstrate varying degrees of disease control and no protocol-defined complete responses. The mechanisms of resistance underlying the lack of more consistent and robust clinical responses to ICI in adults with RRP are poorly understood. Given the currently available results and the risk of immune-related adverse events associated with ICI treatment, the RRPF KOLs feel that ICI use in adults with RRP remains experimental, should only be administered as part of a clinical trial, and that available data does not currently support off-label use of ICIs in the standard-of-care treatment of RRP.
3. Intramuscular injection of the non-specific immune-activating cytokine IFN-α has also been studied for the treatment of RRP, though clinical trials were primarily performed in pediatric populations. Treatment with IFN-α can result in papilloma growth control in a subset of treated patients, but the effect is rarely durable and is often accompanied by significant side effects [49, 50]. For these reasons, the RRPF KOLs have not included off-label subcutaneous IFN-α treatment in the current management algorithm.
4. Peri-lesional submucosal injection of MVA E2, an experimental immunotherapy consisting of a modified vaccinia Ankara vector designed with a DNA payload that encodes the bovine papillomavirus E2 gene, is reported to safely result in durable papilloma disease control following papilloma debulking [51]. The mechanism underlying the observed clinical responses is unclear. The bovine papillomavirus E2 shares less than 37% sequence homology

with HPV 6 or 11 E2 (https://www.uniprot.org/), suggesting that immune responses that may develop targeting bovine papillomavirus E2 after treatment are very unlikely to also target HPV 6 or 11 E2. The reported clinical trial was conducted in Mexico, and whether clinical development of this agent is ongoing is unclear. It is not commercially available. Thus, it was not included in the current management algorithm.

5. Indole-3-carbinol (I3C) is an oral nutritional supplement which is naturally present in high concentrations in cruciferous vegetables. I3C consumption results in a reduction of biologically active estrogen, and estrogen has been historically thought to have a role in RRP pathogenesis [52]. A non-blinded, prospective trial of I3C (in addition to surgical debulking as needed) was performed in a cohort of RRP patients with average follow up of approximately 5 years [53]. No adverse events were observed. Approximately 1/3 of patients had complete response (requiring no additional surgeries during study follow up period), 1/3 had at least a doubling of their pre-treatment inter-surgical interval (partial response), and the remainder were deemed non-responders. It is notable that the complete response group had ~2–3× fewer baseline required surgeries than the partial or non-responders, so confounding effects resulting from RRP heterogeneity cannot be ruled out. Additionally, nearly 25% of the initial cohort was lost to follow-up.
6. In an in vitro study, elevated levels of cyclooxygenase-2 (COX-2) in RRP cultures were found to enhance papilloma growth, while COX-2 inhibition led to papilloma cell apoptosis [54]. Accordingly, celecoxib, a selective COX-2 inhibitor, was studied in a double-blind, randomized, placebo-controlled crossover trial in juvenile and adult onset RRP patients over the course of 2 years per subject (unpublished data reported in clinicaltrials.gov) [55]. There was no statistically significant difference in endoscopic papilloma burden between placebo versus treatment groups. Similarly, there was also no statistically significant difference in subgroup analysis with respect to sex, age of RRP onset, or HPV type (6 versus 11).

4 | Discussion

This Position Statement put forth by the RRPF and their supported KOLs is meant to serve as a clinical guide for the work-up and management of adults with RRP. It outlines a series of diagnostic and therapeutic recommendations based on the pathophysiology of RRP, which is a chronic viral infection of the upper aerodigestive tract. It also aligns with the long-standing desire of patients with RRP to avoid repeat invasive debulking procedures as their primary treatment approach. In fact, the RRP Foundation played a critical role through FDA Listening Sessions in increasing the FDA's awareness of RRP and understanding of the unmet clinical needs for this orphan disease. Creation of this suggested management algorithm which prioritizes medical management as first- and second-line treatment is now possible with the FDA approval of zopapogene imadenovec for adults with RRP and growing experience with off-label use of systemic bevacizumab. These management principles may also apply to juveniles with RRP, but data from prospective immunotherapy and bevacizumab clinical trials specifically designed for pediatric and adolescent populations need to be carefully evaluated by subject matter experts prior to the proposal of an RRPF-sponsored juvenile management algorithm.

These changes in treatment paradigms will take time to implement. But only through general implementation of an agreed-upon management algorithm can we begin to gain significant real-world experience with these new treatment approaches. It is through this process that the treatment will be refined and expanded upon, especially as new treatments become available. For example, if the HPV 6 and 11-specific immunotherapy from Inovio Pharmaceuticals is FDA approved, this would be another immunotherapy option for patients to consider for first-line treatment.

As a Position Statement, this manuscript was authored by RRPF KOLs, and all co-authors were given the opportunity to comment and make suggested revisions. Being listed as a co-author on this manuscript implies agreement with the recommendations provided herein. A more rigorous approach would have been to create a consensus statement using the Delphi method to identify recommendations that gain or do not gain agreement from all or most co-authors. However, Delphi method-informed consensus statements have the prerequisite of the co-authors having extensive experience with the recommendation topics, which is not possible for some of the recommendations made here given the lack of experience with HPV-specific immunotherapy outside of the clinical trial setting. Rather, the RRPF KOLs aimed to create a Position Statement based upon the best available published or publicly-disclosed data and available treatment options, which can be used as a management algorithm moving forward. This allows clinicians caring for adults with RRP to gain valuable clinical experience and the accumulation of valuable real-world data. This proposed management algorithm should also facilitate shared decision-making between patients and their physicians when considering the risks and benefits of all available treatment options.

Financial considerations are an unavoidable topic when discussing new treatment approaches. Despite FDA approval, individual third-party payors will determine coverage policies for newly commercialized HPV-specific immunotherapies. These same payors also set policies for coverage of off-label use of approved treatment such as bevacizumab. Evidence of efficacy, safety, cost-effectiveness, patient advocacy, and corporate efforts such as support assistance will be essential to convince payors to cover these non-surgical treatment modalities and to be able to offer them to as many patients as possible. The RRPF has an important role to play in these endeavors, including direct appeals to Centers for Medicare and Medicaid Services (CMS) for these treatments to be listed as CMS-approved therapies.

5 | Conclusions

It has been over 40 years since RRP was first identified as a chronic HPV-associated infection, and the scientific and clinical contributions of countless known and unknown patients, researchers, surgeons, and clinicians have culminated in an RRP-specific medical treatment. The landmark achievement of an FDA-approved treatment for RRP is a significant milestone for patients, their families, and all providers who have struggled with this disease. This Position Statement and proposed management algorithm are a first step in ensuring that new and non-invasive treatment options such as HPV-specific immunotherapy and systemic bevacizumab are available for all adult patients with RRP.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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