Chapter 10
General discussion and future prospects
GENERAL DISCUSSION

During the past decades, more clinical data on pulmonary arterial hypertension (PAH) have emerged than ever before. Important breakthroughs in adults have furthered the understanding of the pathophysiology, improved diagnosis and led to the availability of targeted treatments for this devastating disease. However, children with PAH have less benefited from these breakthroughs compared to adults, evidenced by unsatisfactory high mortality rates. The field of pediatric PAH suffers from a lack of clinical data on how to tailor and monitor the treatment in the individual child, how to evaluate treatment success during follow-up and how to guide subsequent treatment decisions. The available drugs are barely tested in children as pediatric clinical trial design is hampered by the lack of appropriate clinical endpoints.

In order to improve risk stratification, treatment strategies and clinical trial design for children with PAH, the aims of this thesis were to identify (1) prognostic factors, (2) treatment goals and (3) clinical endpoints in pediatric PAH. In this chapter, the clinical implications of the results of this thesis are discussed, together with directions for future research.

PROGNOSTIC FACTORS

Prognostic factors are clinical or biological characteristics that are objectively measurable and that provide information on the outcome of the disease, e.g. in terms of disease severity and mortality. Prognostic factors are essential for risk stratification and to enable adequate treatment tailoring. First, we systematically reviewed the literature. Chapter 3 identified clinical measurements that were reported to be consistently and significantly associated with mortality in children with PAH: WHO functional class (WHO-FC), serum levels of (N-terminal pro-)B-type natriuretic peptide ([NT-pro]BNP), and four hemodynamic variables obtained by cardiac catheterization. This recapitulation of available data in pediatric PAH did not preclude the potential of the many other variables that have incidentally been shown to correlate with mortality, but rather provided directions for further research to address gaps in evidence. Subsequently, the studies presented in Chapters 4 to 6 have added to the available data that additional clinical measurements, namely echocardiographic variables, a child’s growth, and serum levels of uric acid are also associated with disease severity and/or mortality in pediatric PAH.

As these prognostic factors allow for risk stratification, it is reasonable to utilize them for tailoring the initial treatment in an individual child with PAH. A treatment algorithm has been proposed by the Pediatric Task Force of the 5th World Symposium on Pulmonary Hypertension (WSPH) in Nice in 2013, in which more aggressive treat-
ment regimens are recommended for children at higher risk as assessed according to a suggested list of clinical measurements. Monotherapy with oral endothelin receptor antagonists, oral phosphodiesterase-5-inhibitors or inhaled prostanoids is recommended for lower risk children and combination therapy or parental prostanoids are recommended for higher risk children (see Chapter 2 for more extensive discussion). Given the lack of data on prognostic factors at the time when these clinical measurements were first proposed in 2013, the pediatric task force had to rely on small cohort studies and expert consensus. Which new insights do the findings of this thesis provide with respect to this important topic of risk stratification?

Clinical characteristics

Clinical characteristics that have been suggested for risk stratification at the 5th WSPH include clinical evidence of right ventricular (RV) failure, progression of symptoms, syncope, growth and WHO functional class. The findings of Chapter 3 demonstrate that there is a paucity of data regarding associations with mortality for the first three of these. However, either RV failure, symptoms and syncope are of direct clinical value regarding disease severity, which justifies their use for risk stratification. WHO-FC is a direct disease severity measure also, and the meta-analysis results have shown its association with mortality to be strong and consistent. The prognostic value of 6-minute walk distance (6MWD) in pediatric PAH has been questioned in the past, as infants cannot walk and young children might be easily distracted during the test. However, recent data demonstrate that 6MWD does carry prognostic value in children of 7 years and older, and is therefore of importance for risk stratification and tailoring treatment.

Growth has rightly been proposed for risk stratification, if only in view of the fact that failure to thrive is an alarming sign associated with serious pediatric illness. However, the clinical interpretation of growth measurements is almost impossible without an evidence-based perspective. This especially holds true for pediatric PAH, as concomitant conditions that concurrently affect growth are very common. Assessment of the degree of growth impairment, longitudinal descriptions over time, and the identification of subgroups at risk and associated determinants are all prerequisites for enabling clinicians to make use of growth in the management of children with PAH. The findings of Chapter 5 do not only confirm previous suggestions that growth is a prognostic factor, but also allow for its actual use in clinical practice. Children with Trisomy-21, ex-prematurity and growth-affecting concomitant diseases including congenital heart disease (CHD) are more likely to have growth deficits, but significant growth impairment was also observed in children with idiopathic PAH without any comorbidities. Clinicians observing growth impairment can now use this new information to place growth of an individual child with PAH in context, and assess risk accordingly.
Biological serum markers

Ventricular (and also atrial) wall stress due to volume or pressure overload results in synthesis of the precursor proBNP that is cleaved in the biologically active BNP and the inactive amino-terminal fragment NTproBNP. Serum levels of both BNP and NT-proBNP are closely linked to RV function, which is the main determinant of the clinical course in PAH. Monitoring serum levels of (NT-pro)BNP provides valuable information on the degree to which the RV is capable of coping with the increased afterload due to PAH. Important to consider when interpreting single absolute values of (NT-pro)BNP is the fact that normal serum levels vary by age. In newborns, serum levels are extremely high, with a dramatic decrease in infancy, a mild gradual further decline during childhood and a gradual increase during adulthood. Furthermore, although less relevant in the pediatric setting, levels may increase with renal dysfunction and decrease with obesity. (NT-pro)BNP fluctuations have been demonstrated to accurately track hemodynamic and echocardiographic changes over time in PAH. In Chapter 8 we demonstrate that such fluctuations also carry prognostic value regarding outcome, strongly underlining the usefulness of (NT-pro)BNP as a prognostic biomarker in pediatric PAH.

Uric acid qualifies for risk stratification as well. As a degradation product of purine metabolism, uric acid is increased in oxidative stress conditions such as vascular and cardiac dysfunction. Hyperuricemia is frequently observed in PAH, and has previously been shown to be associated with disease severity and outcome in cross-sectional studies in both children and adults. The extensive longitudinal evaluation of uric acid in pediatric PAH described in Chapter 6, demonstrates that these associations remain consistent during the course of the disease and that a gradual incline in uric acid is an ominous sign associated with poor outcome. In view of their suggested role in vascular remodeling and inflammation, which are important parts of the PAH disease process, purine metabolism and its degradation products have been recognized as interesting candidate biomarkers in PAH for a long time. However, as purine metabolism is involved in many other mechanisms also, hyperuricemia can occur in many circumstances unrelated to PAH. For example, uric acid levels increase in cases of gout, renal dysfunction, treatment with diuretics and insulin resistance. The lack of specificity of uric acid in these settings has depreciated its clinical value in adults with PAH. However, this should not be the case in pediatric PAH as the occurrence of such comorbidities is rare in children.

(NT-pro)BNP and uric acid are not interchangeable as biomarkers, since they represent different aspects of the disease and appear to behave very differently over time. To illustrate this, Figure 1 shows long-term trajectories of uric acid and NT-proBNP of two individual children with PAH from the Dutch Network for Pediatric PH, from time of diagnosis until time of death (patient A: female, diagnosed at age 11 years; patient B: male, diagnosed at age 9 years). In both patients, there is a gradual linear incline of serum uric acid levels over time, already from early stages of the disease, whereas NT-proBNP levels
remain relatively low during the earlier stages and increase more abruptly to its highest levels late in the disease course. These different trends over time are presumably due to the fact that these biomarkers represent different disease aspects: uric acid as a global marker of a child’s gradually declining condition during the full disease course, and NT-proBNP as a more specific marker of RV function with high sensitivity to detect RV decompensation in the advanced disease stage. The importance of monitoring trends of these biomarkers over time rather than interpreting single absolute values is illustrated by a comparison of patient A and B in Figure 1. Especially for uric acid, it appears that changes over time carry much more important information than the absolute uric acid level at any specific time point. Monitoring over time allows a patient to be its own reference, and also allows accounting for natural variability in these markers.

Cardiovascular imaging

The findings of Chapter 4 allow for specific recommendations regarding the role of echocardiography in risk stratification. Based on our results and also confirmed by findings of Jone et al,16 right-to-left ventricular (RV/LV) diameter ratio is a reliable and easily obtainable echocardiographic prognostic factor in pediatric PAH, that incorporates both pathologic septal shift and RV enlargement. RV ejection time and tricuspid annular plane systolic excursion (TAPSE) are indicators of RV function and are now both also demonstrated as prognostic factors. Another important new insight from Chapter 4, is the fact that reduced left ventricular (LV) dimensions have prognostic value as well. An interesting unanswered question is whether the smaller LV in advanced PAH is a result of an imbalanced RV/LV ratio due to compression by a dilated high-pressure RV and prolonged systolic RV contraction, or whether this is explained by ventricular interdependence-related failure of the LV structure and function.

Chapter 3 shows that cardiac magnetic resonance imaging (CMR) has not yet been sufficiently studied to allow recommendations for its use in risk stratification in
children with PAH. Even in adult PAH, only few studies have assessed CMR in predicting outcome. The quality of obtainable images is superior to echocardiography and allows for an extensive assessment of RV structure and function. Drawbacks are the reduced feasibility in young children without sedation or general anesthesia, and the limited accessibility to required infrastructure and expertise on a global scale. Nevertheless, CMR is a promising modality in pediatric PAH and studies are currently ongoing to evaluate its value as indicator of disease severity and prognosis.

**Cardiac catheterization**

*Chapter 3* convincingly demonstrates the prognostic importance of the conventional hemodynamic variables pulmonary vascular resistance (PVR), mean right atrial pressure, cardiac index and acute response to vasodilator testing. This strongly supports the role of hemodynamics for risk stratification at time of diagnosis.

In addition to their role as prognostic factors for risk stratification in advanced PAH, hemodynamics are also used in specific settings where a patient is at risk for future development of advanced PAH. This is the case in children with CHD in whom early pulmonary vascular disease (PVD) has developed due to increased pulmonary blood flow. In these circumstances, clinical decision making regarding operability is a particular challenge. Conventionally, PVR and sometimes also mean pulmonary arterial pressure (mPAP) are used to guide therapy decisions such as whether and when a cardiac defect should be repaired or when PAH-targeted therapy should be initiated. The 20-year follow-up study presented in *Chapter 7* confirms previous findings that conventional hemodynamics are very useful but lack accuracy in predicting disease progression, re-emphasizing the need for complementary measurements that provide additional insight in the state and dynamics of the pulmonary vasculature. Main findings of the study were that indices of pulmonary arterial (PA) stiffness, measured by intravascular ultrasound during cardiac catheterization, provide information on vascular wall dynamics that carry prognostic value regarding disease progression and outcome in children with PVD, also in settings of a favorable hemodynamic profile (i.e. relatively low PVR and/or mPAP).

Watching the actual disease development more closely rather than relying on the hemodynamic effects of PVD, probably allows for better prognostication of disease progression. Conventional measurements obtained during cardiac catheterization show the hemodynamic consequences of PVD, rather than the disease itself. However, increased PA stiffness is at least partly explained by the hemodynamic consequences of PAH as well, since increases in PAP mechanically increase PA wall stiffness by moving the artery wall to a higher point on the volume/pressure curve. Nevertheless, PA wall stiffening is also inherently part of the disease process of PAH. Hence, PA stiffness indices incorporate valuable information on both hemodynamic consequences and the pathological process, which may explain the prognostic value that we found in settings
of still favorable hemodynamics. Therefore, Chapter 7 suggests assessment of PA stiffness as a complement to conventional hemodynamics, to improve prediction of disease progression in such settings.

In the studied cohort, patients who underwent shunt closure all showed subsequent reversal of PVD. Therefore, the results of Chapter 7 could not inform whether PA-stiffness indices can predict adverse effects of shunt closure. There is a great clinical need of data on how to assess operability, as there is a substantial population of patients with PAH after shunt closure that have a dismal prognosis when compared to other forms of CHD-associated PAH. On the other hand, there is also a population of CHD-associated PAH whose shunt should have been closed to prevent progression of PVD. Already for many years, pediatric and congenital cardiologists debate on how to assess operability based on cardiac catheterization, in the absence of randomized controlled data. Patients with an indexed PVR (PVRi) < 6 WU*m^2 are considered safe for surgery by some clinicians. A PVRi between 6 and 9 is considered borderline, and although controversial, acute vasodilator testing is encouraged to help decide whether a patient is operable in those cases. More recently, a PVRi of 4 WU*m^2 was proposed as the limit for operability, and a PVRi of 4-8 WU*m^2 as the borderline range. Empirical data supporting any of the proposed cut-offs are extremely limited. Therefore, clinicians agree that assessment of operability is a matter of discussion on an individual basis, in which not only hemodynamic cut-off values but the whole diagnostic scenario of a patient has to be taken into account, e.g. including the type of cardiac defect, clinical history and functional status.

**TREATMENT GOALS AND CLINICAL ENDPOINTS**

The prognostic factors as put forth in Chapters 3 to 6 are useful in risk stratification in PAH. An important additional question, which was a particular focus in Chapters 8 and 9, is whether and how such clinical measurements may be used to evaluate treatment efficacy throughout the disease course, either in clinical practice or clinical trial design. Among both clinicians and regulators, there is consensus that an outcome measurement to evaluate treatment efficacy should be clinically meaningful, directly measuring how a patient feels, functions or survives. Alternatively, indirect surrogates of such clinically meaningful outcomes may qualify.

Treatment goals may be regarded as the treatment efficacy measurements for clinical practice, and clinical endpoints are the treatment efficacy measurements for the specific setting of a clinical trial. The concept of a treatment goal, which is becoming widespread in the field of PAH, has been introduced in Chapters 1 and 2 as a predefined improvement of a measurement that is the direct equivalent of a clinically meaningful
outcome (e.g. relieve of symptoms), or a predefined improvement of a measurement that serves as an indirect surrogate for a clinically meaningful outcome (e.g. representing a decrease in the chance of mortality). Prior to reviewing the yield and implications of this thesis regarding treatment goals and clinical endpoints, direct and indirect (surrogates for) clinically meaningful outcomes are discussed.

**Direct clinically meaningful outcomes**

Multiple aspects of routine clinical history taking and physical examination of children with PAH are directly clinically meaningful. For example, PAH symptoms like dyspnea, chest pain or syncope are direct indicators of how a patient feels and hence are clinically meaningful. This also holds true for WHO-FC, growth status, physical activity level (e.g. measured with accelerometer) and 6MWD, being indicators of patients’ ability to function in daily life. For each of these clinical measurements, reliability needs to be carefully considered for each individual patient as some of these may be susceptible to subjectivity, clinical judgment and motivational issues. Obviously, the disease course of a patient (i.e. “how a patient survives”) is also clinically meaningful, including the rate of disease progression, need for additional therapies (intravenous prostanoids, atrial septostomy, Potts shunt, (heart-)lung transplantation), and mortality. Although event rates of such occurrences may qualify as study outcomes, the irreversible nature of these events hampers their usefulness for clinical decision making.

Most of the diagnostic variables commonly used in the follow-up of children with PAH do not provide directly clinically meaningful outcomes. For example, echocardiography and cardiac magnetic resonance imaging can yield important measurements regarding the severity of the disease and prognosis, but none of these measurements does directly represent how a patient feels, functions or survives. Similarly, highly prognostic hemodynamic variables obtained during cardiac catheterization or laboratory biomarkers are not directly clinically meaningful for a patient.

**Surrogates for clinically meaningful outcomes**

Diagnostic variables that are not directly clinically meaningful might still qualify for the evaluation of treatment efficacy, provided that they are valid surrogates for a true clinically meaningful outcome measure. The results of this thesis have revealed that echocardiographic and hemodynamic measurements and laboratory values prognosticate disease severity and survival, which are outcomes that are both clinically meaningful. However, a correlation with outcome does not always indicate surrogacy. In addition to a strong correlation with outcome, there are two additional basic characteristics of a surrogate: (1) the measurement is modifiable by treatment and (2) treatment-induced changes in the measurement correlate with changes in outcome as well. A “true” surrogate is part of the causal pathway of the disease, which in theory can be validated
by testing whether influences on the final clinically meaningful endpoint are causally explained by influences on the surrogate, requiring extensive modeling in very large prospective cohorts that are not available in the field of (pediatric) PAH. Nevertheless, this should not distract from the vital first step in surrogacy validation, which is the evaluation of changes of prognostic factors over time. Which of the prognostic factors can be improved by treatment, and do such improvements predict improved outcome?

The study in Chapter 8 aimed to answer this specific question by investigating the prognostic value of treatment-induced changes in a set of noninvasive prognostic factors. The results revealed that WHO-FC, NT-proBNP and TAPSE were modifiable prognostic factors of which changes over time were associated with survival. This suggests that these three clinical measurements are not only simple predictors of outcome, but also hold promise as surrogates for survival. As improvements of WHO-FC, NT-proBNP and TAPSE appear to lead to better outcomes, it seems reasonable to consider the striving for these improvements as prognostically relevant.

In this same line of reasoning, it deserves speculation that growth and uric acid qualify as surrogates as well. An important finding of Chapter 5 was that Z-scores for height could improve throughout the disease and that catch-up growth was independently associated with a favorable disease course (a clinically meaningful outcome). In addition to demonstrating the prognostic value of serum levels of uric acid (both at baseline and throughout the disease), Chapter 6 showed that deteriorations and a gradual incline in uric acid are associated with worse outcome. As changes of both height-for-age Z-score and uric acid over time appear to lead to changes in outcomes, it seems of added value to monitor these clinical variables and strive for their improvement.

**Treatment goals**

The identification of treatment goals allows for the development of goal oriented treatment strategies for pediatric PAH. In adult PAH-patients, a goal-oriented treatment strategy is recommended, in which validated clinical and laboratory variables are used to guide the clinician in the timing of therapy escalations or lung transplantation. A goal oriented treatment strategy appears the most appropriate in a progressive incurable disease like PAH, since the conventional “waiting for clinical deterioration” leads to lagging behind events. During the 5th WSPH, potential treatment goals for a pediatric goal oriented treatment strategy have been suggested, based on expert opinion (introduced in Chapter 2).

When improvement of quality of life (directly clinically meaningful for a patient) is the overall objective of such a goal-oriented treatment strategy in pediatric PAH, then all direct indicators of how a patient feels or functions directly qualify for its use as treatment goals. For example, these include PAH symptoms, WHO-FC, growth status,
and 6MWD. Cut-offs in these variables can be predefined according to a desired target level of symptom relieve or functional abilities, allowing for its clinical applicability as treatment goals.

However, when improvement of outcome is the overall objective (or part of the objective), then the data regarding surrogacy validation becomes highly essential. This thesis provides clues regarding the surrogacy of WHO-FC, NT-proBNP, TAPSE, growth and uric acid. For the first three of these, prognostically relevant cut-offs were determined as part of Chapter 8, to allow definition of clinically applicable treatment goals. It was demonstrated that reaching values below the identified cut-offs for WHO-FC (≤III) and NT-proBNP (≤1200 ng/L) and above the cut-off for TAPSE (≥12 mm) during follow-up, indeed correlated with better survival rates. Failing to reach values below (WHO-FC and NT-proBNP) or above (TAPSE) these thresholds resulted in significantly worse survival, suggesting that treatment should be escalated rapidly in these children.

With respect to the identification of treatment goals, an understudied area is cardiac catheterization. Data regarding the prognostic values of changes in hemodynamics are absent in children.

**Clinical endpoints**

In both adult and pediatric PAH, there is ongoing debate regarding the optimal selection of endpoints for clinical trials. In adults, the 6MWD and hemodynamics have been the most frequently used endpoints in clinical trials. Although children as young as three or four years of age may be able to do a 6-minute walk test, a reliable performance cannot be expected under the age of seven or eight years. Invasively mPAP and PVR are objective and robust measurements, but obtaining hemodynamic data carries a risk in children. Besides, hemodynamics are not directly clinically meaningful for a patient, and its surrogacy for survival has been questioned in adults.

Do the non-invasive treatment goals identified in Chapter 8, WHO-FC, NT-proBNP or TAPSE, also qualify as potential trial endpoints for children? WHO-FC is both clinically meaningful and a powerful prognostic factor, but its reliability depends on what the patients or parents tell the treating physician. Another drawback is the categorical nature of the variable, which hampers the detection of subtle changes, especially for patients who are in WHO FC II or III. Also, WHO-FC is susceptible to ceiling and flooring effects, as patients in WHO-FC IV cannot deteriorate and in WHO-FC I cannot improve. NT-proBNP and TAPSE are not directly clinically meaningful for a child, but the demonstrated prognostic value of changes over time provides important clues for surrogacy. Both are attractive as potential endpoints, as both measurements are easily obtainable and can be repeated as many times as needed. Prior to installment as an endpoint, further research is desired on sensitivity and specificity, and on how to deal with variations in age.
The clinical worsening (CW) endpoint as presented in Chapter 9 of this thesis, has gained increasing interest. The most important advantage is that it is patient-centered, and consists of clinically meaningful components only. The results of the validation study show high event rates and a strong correlation of the soft components with outcome, which support its potential as a composite clinical endpoint. Important prerequisites to guarantee its reliability and comparability throughout trials, are the installment of independent adjudication committees and the agreement on a uniform endpoint definition. A general caveat of composite endpoints is reduced interpretability compared to single endpoints, especially when the incorporated components have different clinical meaning. In frequently used and well-established clinical trial endpoints in cardiovascular disease, such as the Major Cardiovascular Event composite endpoint, all components represent irreversible morbidity and mortality (cardiovascular death, stroke or myocardial infarction). For the CW endpoint, some of the components indicate irreversible morbidity/mortality, but not all. For example, deteriorations in WHO-FC and 6MWT indicate clinical worsening, but this might be reversible. Also, hospitalizations for PAH do not necessarily indicate irreversible morbidity. When CW is considered as an endpoint for trials in PAH, it is important that these drawbacks will be taken into account.

Other potential clinical endpoints for pediatric PAH that have not been studied in this thesis but are interesting include CMR and ambulant physical activity monitoring. In pediatric PAH, the available data on the prognostic value of CMR variables is limited. In adults with PAH, changes in RV functional CMR measurements have been shown to correlate with outcome, pointing in the direction that such measurements might have potential as survival surrogates. Longitudinal studies in children are needed to evaluate whether CMR variables might qualify as surrogates for clinically meaningful outcomes. Ambulant physical activity monitoring using accelerometer recordings seems suited ideally to children to measure changes in physical activity in response to therapy. The data from the recordings are directly clinically meaningful, as they are expected to represent a child’s functional capacity. Studies are currently ongoing to evaluate its value as indicator of disease severity and prognosis in pediatric PAH, and its usefulness as clinical trial endpoint.

**CONSIDERATIONS AND FUTURE PROSPECTS**

PAH is a heterogeneous disease, which poses challenges for any study to be conducted in this field. A “one-size-fits-all approach” is outdated in medicine, with personalized precision medicine becoming the new standard. This especially seems the way to go in the field of PAH with multiple heterogeneous phenotypes. One must remind, however, that the goal of individualized medicine can only be achieved by large patient-based
General discussion and future prospects

International registries such as Tracking Outcomes and Practice in Pediatric PH (TOPP) are ideally suited to characterize patients and detect subgroup differences in therapy response and clinical disease course. In a rare disease like PAH, it is of importance that treatment strategies and collection of clinical parameters are standardized, to allow reliable conclusions from such observational data. As registries are labor-intensive and costly, they should be designed adaptive. For example, when there are new insights regarding potential biomarkers or when there are clues that a certain treatment strategy is superior to the conventional one, case report forms of the registry can be adjusted to allow timely capture of such potential important information.

We have proposed prognostic factors that seem suitable for risk stratification in children with PAH. When considering the proposed prognostic factors, it of great future interest which of the clinical measurements carry independent predictive value above the other ones. This could be evaluated in larger datasets, which may be achieved by international collaboration. It was not studied whether the actual use of these prognostic factors in clinical practice leads to better management outcomes. Similarly, the treatment goals have been identified based on solid data, but whether its incorporation in goal oriented treatment strategies translates into better outcomes remains to be demonstrated. Prospective, preferably randomized, studies are desired to evaluate the comparative effectiveness of conventional treatment strategies and newly proposed ones. As an example, many clinical trials have been conducted in patients with heart failure, to show that NT-proBNP guided treatment leads to better outcomes than conventional treatment strategies, independent of the received heart failure medication. Such studies may be challenging in PAH due to small patient numbers, but well-designed prospective observational studies can already provide valuable information on this topic.

The data that support valid clinical endpoints now allow for the design of clinical trials in pediatric PAH. To achieve the number of required children, international collaborations will be necessary. In view of the drawbacks of CW as an endpoint, the quest for suitable pediatric endpoints must continue.

CONCLUDING REMARKS

The studies described in this thesis provide prognostic factors, treatment goals and potential clinical endpoints for the field of pediatric PAH. The presented data constitute a substantial and highly needed step towards better risk stratification, treatment strategies and clinical trial design for this delicate patient population. The limitations and newly arisen questions of this thesis underline the huge amount of work that remains to be done, but increasing international collaborations among PH experts and promising
diagnostic and therapeutic developments do bring hope for the children and families that have to cope with this devastating disease.
REFERENCES


