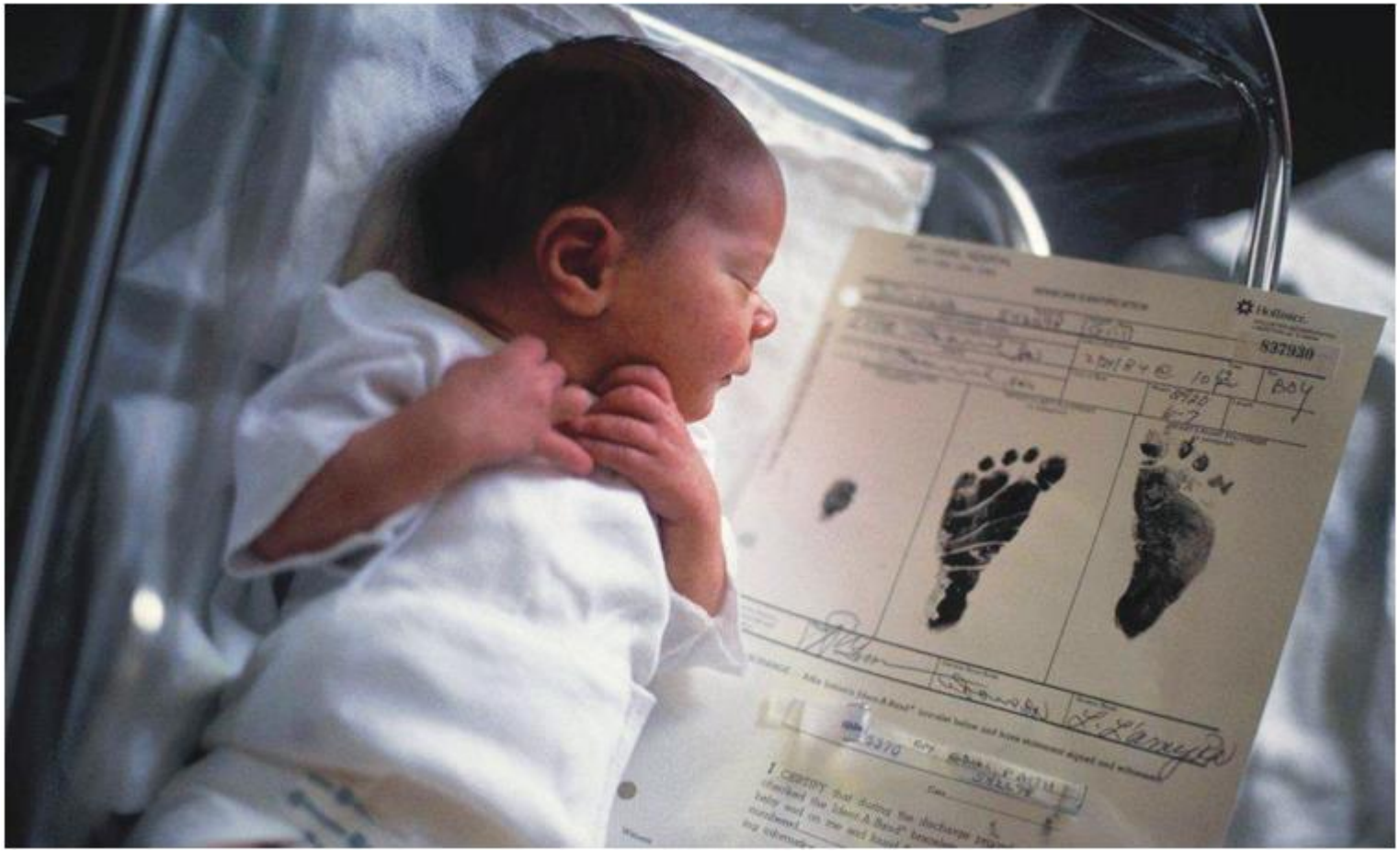
Nebraska Newborn Screening Program
Quick Reference Guide



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Purpose of this Guide

Information for this Quick Reference Guide has been partially taken from the latest edition of the Nebraska Newborn Screening Program, Practitioner's Manual. This guide is meant to be a quick reference rather than the more comprehensive Practitioner's Manual. This is not meant to take the place of the manual as there is information in the Practitioner's Manual that is vital to a more complete understanding of the Nebraska Newborn Screening Program and the role practitioner's play in this life saving system. The Quick Reference Manual is created with the awareness that busy Practitioners often need an answer to a question to be available in a more accessible format. More complex questions will be answered by referring to the Practitioner's Manual.

The Nebraska NBS statute and regulations place the responsibility for educating parents, obtaining a newborn screening specimen and following up on newborn screening results in the hands of the Practitioners caring for the babies. The Newborn Screening Advisory Committee and the Newborn Screening Program Staff wish to support Practitioners as they care for babies and fulfill their responsibilities relating to newborn screening.

Newborn Blood Spot Screening in Nebraska

In Nebraska all babies are required by law to have a blood spot screen. There is no waiver available to allow refusal of the screening.

Physicians are responsible for educating parents about newborn screening and the NBS Program supplies free of charge a comprehensive brochure to aid in this process. The "Parent's Guide to Your Baby's Newborn Screening" is also provided to birth facilities and to prenatal health care providers.

To screen babies for the required conditions, five drops of blood must be collected via heel stick on to the filter paper between 24 and 48 hours of age. The attached Collection and Reporting (CARe) form must be filled out completely and legibly in order to provide the needed information for testing and follow up. The specimens must be allowed to air dry and then are shipped (within 24 hours of collection) over night to the screening laboratory PerkinElmer Genetics in Pittsburgh, PA.

In lab testing is usually completed in 1.5 days. Some results may be available earlier. The testing may take longer when results indicate the need for repeat or reflex testing. When all tests are completed the results are sent back to the hospital where the specimen was drawn. These results are passed on to the ordering physician.

If follow up is required, the lab will notify the baby's health care provider, the newborn screening program and the hospital. Depending on the actions required for follow up, the staff of the NBS program will contact the provider via fax or fax and phone. In the cases where confirmatory testing is needed, the program staff will provide direction regarding the specific tests and referrals that will be needed. Certain results will be reported to a subspecialist in order to facilitate the appropriate follow up.

The Nebraska NBS Program attempts to obtain the name of the provider who will be seeing the baby as well as the provider who orders the NBS on the CARe form. If there is no information available about a provider other than the one ordering the test, that provider is responsible for all follow up.

The NBS program staff will follow babies with abnormal results until they receive all testing necessary for diagnosis. In the cases that only require a repeat NBS the results will be available to the program. When confirmatory testing is required, the program will be requesting the results from the provider as well as the diagnosis and treatment started if any.

Please contact the NBS program with any questions you have about the screening process, results, or recommendations. The staff can be reached at (402) 471-0374. The protocols used by the program have been created with the assistance of the NBS Advisory Committee and the appropriate Pediatric Specialists.

The staff of the NBS program is available after hours, consistent with the laboratories operating hours. The number to call is (402) 471-0374.

Urgency and Newborn Screening

When Newborn Screening began it was for Phenylketonuria (PKU). While the prompt initiation of the appropriate diet is very important, patients did not face a life threatening crisis if screening was delayed by a day or two.

Currently the newborn screening panel contains conditions that can be life threatening soon after birth. Some positive screens should be considered neonatal emergencies and responded to immediately. Lack of screening and a lack of an appropriate response to positive results may lead to permanent damage or death for a baby.

When a baby does not receive a screen or the specimen collected is unsatisfactory for testing, we cannot know if the baby has one of the time critical conditions.

In all cases it is important to respond to the results of a newborn screen in a timely way in order to maximize the benefits of the newborn screening system.

Conditions on Nebraska Screening Panel	Common Abbreviation
3-Hydroxy 3-Methyl Glutaric Acidurea	HMG
3-Methylcrotonyl-CoA Carboxylase Deficiency	3-MCC
Argininosuccinic Acidemia	ASA
Beta-ketothiolase Deficiency	BKT
Biotinidase Deficiency	
Carnitine Uptake Defect	CUD
Citrullinemia	CIT
Congenital Adrenal Hyperplasia	CAH
Congenital Primary Hypothyroidism	CPH
Cystic Fibrosis	CF
Galactosemia	
Glutaric Acidemia Type 1	GA 1
Hemoglobinopathies: SS disease, SC disease, S-Beta Thalassemia	
Homocystinuria	HCY
Isovaleric Acidemia	IVA
Long-Chain Hydroxyacyl-CoA Dehydrogenase Deficiency	LCHAD
Maple Syrup Urine Disease	MSUD
Medium Chain Acyl Co-A Dehydrogenase Deficiency	MCAD
Methylmalonic Acidemia: Mutase	MUT
Methylmalonic Acidemia: Cobalamin Disorders	Cbl A, B
Multiple Carboxylase Deficiency	MCD
Phenylketonuria	PKU
Propionic Acidemia	PA
Severe Combined Immune Deficiency	SCID
Trifunctional Protein Deficiency	TFP
Tyrosinemia	TYR
Very Long-Chain Acyl-CoA Dehydrogenase Deficiency	VLCAD

Condition	Abnormal Test Results	Likely Causes	Provider Follow Up Actions
Biotinidase Deficiency	POSITIVE ≤ 8.0 ERU (enzyme reaction units) INCONCLUSIVE 8.1 < 16 ERU	-Biotinidase deficiency -Partial Biotinidase deficiency -Enzyme in specimen denatured by heat and/or humidity -False positive	-POSTIVE: Notify parents, and obtain confirmatory serum specimen per program protocol (specifics will be communicated via phone.) Consult with pediatric metabolic specialist. Report lab tests, diagnosis and treatment to Program. -INCONCLUSIVE: Notify parents, and obtain repeat dried blood spot testing. Most often levels will normalize on repeat. If on repeat levels are still low, consult with and/or refer to pediatric metabolic specialist.
Congenital Adrenal Hyperplasia (CAH)	POSITIVE 17-OHP above the critical cut-off for weight range and baby is > 2500g. Extracted assay to be run. PRELIMINARY POSITIVE 17-OHP above the critical cut-off for weight range but baby is < 2500 g. Extracted assay run. If elevated, report amended to POSITIVE. If normal report amended to WNL. INCONCLUSIVE 17-OHP above reference range, but not above the critical cut-off. Extracted 17-OHP above reference range.	(applies to all abnormal results) Salt-wasting CAH -Simple virilizing CAH -False positive -Prematurity or stress	-POSTIVE: Possible neonatal emergency. Consult with pediatric endocrinologist. Notify parents, evaluate newborn immediately and consider admit to hospital for monitoring. Order confirmatory serum specimen for steroid profile and monitor electrolytes. Ensure steroid profile is tested at laboratory with established neonatal reference ranges. Report lab tests, diagnosis and treatment to NBS Program -PRELIMINARY POSITIVE: If NICU admission monitor electrolytes, watch for signs/symptoms. If discharged to home contact parents and assess status. Contact pediatric endocrinologist if concerns. If POSITIVE after extracted result is reported, follow steps as above for POSITIVE. INCONCLUSIVE. Obtain repeat dried blood spot specimen. Assess infant.

Congenital Primary Hypothyroidism (CPH or CH)	POSITIVE T4 low/TSH elevated	-Hypothyroidism -False positive -Prematurity (transient hypothyroidism or hypothyroidism of prematurity)	POSTIVE: Notify parents, and obtain confirmatory serum specimen, serum Free T4 and TSH. Ensure specimen is tested at laboratory with established neonatal reference ranges. Consult with pediatric endocrinologist. Report lab test results, diagnosis and treatment to NBS Program.
	WNL for CPH but T4 low/ TSH normal	•Thyroid Binding Globulin Deficiency (TBG) deficiency •False positive for TBG deficiency •Hypothalamic or Pituitary gland problems with secondary or tertiary hypothyroidism •Prematurity	For purposes of screening for congenital primary hypothyroidism, this result is normal.
	WNL for CPH but T4 high/ TSH elevated	-Hyperthyroidism (extraordinarily rare in infants)	For purposes of screening for congenital primary hypothyroidism this result is normal.
Cystic Fibrosis (CF)	POSITIVE due to elevated IRT and two CFTR mutations or meconium ileus with two CFTR mutations	CF, CRMS, CF carrier state	POSITIVE - Refer to Accredited CF Center for evaluation and sweat testing
	INCONCLUSIVE due to elevated IRT but no copies ΔF508 mutation	CF, Asphyxia, Trisomy, prematurity, liver or GI dysfunction, CF carrier state, CFTR-Related Metabolic Syndrome (CRMS)	INCONCLUSIVE - Repeat NBS to recheck IRT as directed

Cystic Fibrosis (CF) continued	INCONCLUSIVE due to repeat elevated IRT and one or less mutations	CF, asphyxia, Trisomy, prematurity, liver or GI dysfunction, CF carrier, CRMS	INCONCLUSIVE - Refer to Accredited CF Center for evaluation
	INCONCLUSIVE due to elevated IRT with one copy of ΔF508 mutation	CF, CF carrier state, CRMS, lab error	INCONCLUSIVE - Refer to Accredited CF Center for evaluation and sweat testing
	INCONCLUSIVE due to meconium ileus/bowel obstruction with one or less mutations	Inconclusive due to meconium ileus/bowel obstruction with one or less mutations	INCONCLUSIVE - Refer to Accredited CF Center for evaluation and sweat testing
Galactosemia	POSITIVE – Elevated Galactose, Low Uridyl transferase	-Severe galactosemia -Improperly collected sample (heat damage or transit delay) -Mild galactosemia variant -Other enzyme defect in RBC's -False positive	POSITIVE: Potential Neonatal Emergency. Consult with pediatric metabolic specialist. Contact parents and obtain serum confirmatory test for galactose-1-phosphate uridyl-transferase. Interrupt breast or mammalian milk formula and initiate powder- based soy formula. Report lab tests, diagnosis and treatment to NNSP.
	Inconclusive - Elevated Galactose, Normal GALT	(same as above)	Inconclusive: Contact parents and obtain repeat dried blood spot specimen testing. Most often repeats will be normal. If galactose is still elevated on repeat, refer to pediatric metabolic specialist.

Hemoglobinopathies	FS	-Hemoglobin S-S Disease -Sickle-β Thalassemia	For all clinically significant abnormal results: -Confirm via repeat NBS or other testing -Refer to Pediatric Hematologist -Offer Genetic Counseling to Family -Report results back to NE NBS Program
	FSA	-Sickle β Thalassemia	
	FC	-Hemoglobin C Disease	
	FSC	-Hemoglobin S-C Disease	
	F only	-β Thalassemia Major -Very Premature Baby -Hereditary Persistence of Fetal Hemoglobin	
	FE	-Hemoglobin E Disease -Hemoglobin E-β Thalassemia	
	FV	-Homozygous Variant - Variant-β Thalassemia	
	AF	-Older child not producing as much F -Post transfusion	-Verify age and status of infant -If necessary consult Pediatric Hematologist or NE NBS Program for follow up recommendations
	FA + Bart's	-Hemoglobin Bart's -False Positive	-Confirmatory Testing -Follow up per algorithm provided by Program -Consult Pediatric Hematologist as needed
	FAV	-Hemoglobin Variant Trait	-Confirmatory testing -Follow up per algorithm provided by Program - Consult Pediatric Hematologist as needed

Hemoglobinopathies (cont.)	FAS FAC FAE FAD FAO$_{Arab}$	Sickle Cell Trait Hemoglobin C Trait Hemoglobin E Trait Hemoglobin D Trait Hemoglobin O$_{Arab}$ Trait	For all of the following Traits: -Confirmatory Testing -Consult Pediatric Hematologist as needed -Offer Family Genetic Counseling
Severe Combined Immune Deficiency (SCID)	Positive	SCID Other conditions with T cell lymphopenia False Positive	POSITIVE -Referral to Immunologist on call for SCID NBS -Confirmation via flow cytometry as directed -CBC also needed -Isolate baby as directed by Immunologist -Stop breast feeding until Mom's CMV status is determined -Refrain from administering live virus vaccines -If transfusion required, use only CMV negative, leukoreduced, irradiated products
	Inconclusive	Prematurity	INCONCLUSIVE Follow up as directed – repeat collection of NBS at directed time or confirmatory testing may be requested
	Failure to Amplify	Poor Sample Quality Sample contaminated	FAILURE TO AMPLIFY – Repeat collection of NBS or confirmatory testing may be requested

Conditions Detected by Tandem Mass Spectrometry (MS/MS)	Results fall into four categories: • Substantial elevations • Moderate elevations • Slight elevations • Repeat specimen remains elevated	Abnormal analyte levels due to condition on screening panel Analyte levels increased due to condition not on screening panel False positive with analyte levels increased not due to a disease False positive with analyte levels increased due to maternal condition or interference of various treatments of the infant	SUBSTANTIAL ELEVATIONS: Potential neonatal emergency -Consult with Metabolic Sub Specialist -Contact family and assess child's status -obtain confirmatory testing as directed by specialist MODERATE ELEVATIONS: -Collect NBS for repeat testing in time frame suggested by lab and program – usually within 48 hours -Consult with Metabolic Sub Specialist as needed SLIGHT ELEVATIONS: -Collect NBS for repeat testing in time frame directed by the NBS program - Consult with Metabolic Sub Specialist as needed REMAINS ABOVE NORMAL: -Collect NBS for repeat or confirmatory testing in time frame directed by the NBS program - Consult with Metabolic Sub Specialist as needed
Amino Acidopathies: -Argininosuccinic Acidemia -Citrullinemia -Homocystinuria -Maple Syrup Urine Disease -Phenylketonuria -Tyrosinemia	Elevations of analytes or relative ratios of analytes on **Amino Acid Profile**		
Fatty Acidopathies: -Carnitine Uptake Defect -Medium Chain Acyl CoA Dehydrogenase Deficiency -Long Chain Hydroxyacyl-CoA Dehydrogenase Deficiency	Elevations of analytes or relative ratios of analytes on **Acylcarnitine Profile**		

-Trifunctional Protein Deficiency -Very Long Chain Acyl CoA Dehydrogenase Deficiency **Organic Acidopathies:** -Beta-ketothiolase Deficiency -Glutaric Acidemia Type 1 -Isovaleric Acidemia - Methylmalonic acidemia (methylmalonyl-CoA mutase) - Methylmalonic acidemia (cobalamin disorders) - Multiple Carboxylase Deficiency -Propionic Acidemia -3-Methylcrotonyl-CoA Carboxylase Deficiency -3-Hydroxy 3-Methyl Glutaric Acidurea	Elevations of analytes or relative ratios of analytes on **Acylcarnitine Profile** Results fall into four categories: • Substantial elevations • Moderate elevations • Slight elevations • Repeat specimen remains elevated	Abnormal analyte levels due to condition on screening panel Analyte levels increased due to condition not on screening panel False positive with analyte levels increased not due to a disease False positive with analyte levels increased due to maternal condition or interference of various treatments of the infant	See previous page

Babies in NICU

In 2011 the Nebraska Newborn Screening Program adopted via state regulation, the Clinical and Laboratory Standards Institute's guidelines for screening of premature, low birth-weight and sick newborns admitted to neonatal intensive care units (I/LA-31-A).

- If a baby is to be transferred to another facility, a NBS must be collected prior to the transfer.
- Upon admission to an NICU a NBS must be collected prior to any treatment (exception: respiratory) unless it is verified that one was collected prior to arrival in the NICU; for babies admitted for observation who are not receiving any other treatments the NBS should be drawn at 24-48 hours of age.
- If baby's first NBS was collected prior to 24 hours of age, a repeat NBS should be drawn between 48-72 hours. (Note: NBS from babies less than 24 hours old at collection are not tested for CAH, CF or CPH).
- Babies who weigh less than 2000 grams at birth must also have a NBS drawn at discharge or 28 days of age, whichever is first.

Transfusions and NBS

Transfusions may interfere with the ability to screen blood for conditions on the NBS panel. **Therefore, prior to transfusing a baby a NBS dried blood spot specimen must be collected.**

The Nebraska Newborn Screening Advisory Committee has said that specimens that are greater than 24 hours post transfusion may be considered adequate for testing, except for hemoglobinopathies.

If a baby's first NBS was collected prior to 24 hours of age (and prior to transfusion) a repeat NBS must be collected. The repeat NBS must be greater than 24 hours post transfusion or another specimen will be requested.

If a baby does not have a NBS collected and tested prior to transfusion a repeat NBS will be needed at greater than 120 days post transfusion.

If a baby had a NBS collected but the specimen was unsatisfactory for testing for the hemoglobin and a transfusion occurred in the interim, a repeat NBS will be required at greater than 120 days post transfusion.

Program Contacts

Newborn screening follow-up: (402) 471-0374
This line is connected to a pager answered after hours, weekends and holidays.

Newborn screening fax: (402) 471-1863

Julie Luedtke, Program Manager - (402) 471-6733
Krystal Baumert, Follow Up Coordinator - (402) 471-0374
Karen Eveans, Follow Up Specialist (402) - 471-6558
Sarah Seberger, Follow Up & QA Specialist - (402) 471-6759
Angie Groff, Administrative Assistant - (402) 471-9731

Nebraska Newborn Screening Program Web Site:
www.dhhs.ne.gov/publichealth/pages/nsp.aspx

Testing Laboratory Contacts

PerkinElmer Genetics, Inc
(412) 220-2300

P.J. Borandi, Vice President and General Manager
Joseph Quashnock, PhD, Laboratory Director
Susan Felinczak, Client Services
James DiPerna, PhD, Team Lead, Tandem Mass Spectrometry
Tracy Koger, Team Lead Biochemistry
Zhili Linn, MD, Molecular
Bethany Sgroi, MS, CGC
Meredith Patik, MS, CGC
Lucy Andrews, MS, CGC

Resources and References

The Nebraska Newborn Screening Practitioners Manual with more in depth information is available on the NBS website at:
www.dhhs.ne.gov/publichealth/pages/nsp.aspx

Other Websites with NBS information:
www.babysfirsttest.org
https://www.newsteps.org/
http://www.cdc.gov/ncbddd/newbornscreening/index.html
ACMG Act sheets http://www.acmg.net
Genetic Home Reference http://ghr.nlm.nih.gov

181 NAC 2: REGULATIONS GOVERNING SCREENING OF INFANTS FOR METABOLIC DISEASES at
www.dhhs.ne.gov/publichealth/pages/nsp.aspx

NEBRASKA REVISED STATUTES § 71-519 TO 71-524 at
www.dhhs.ne.gov/publichealth/pages/nsp.aspx

"Newborn Screening Fact Sheets", Celia I Kaye and the Committee on Genetics, PEDIATRICS 2006; 1 18;934-963
http://www.pediatrics.org/cgi/content/full/118/3/e934

"Newborn Screening of Premature, Low Birth Weight and Sick Newborns, Approved Guideline", CLSI I/LA 31-A, 2009

"Toward a Uniform Newborn Screening Panel" Genetics in Medicine, May 2006, Vol 8, Supp 1

Medical Consultants

Medical consultants are available to provide consultation for the follow-up, evaluation, and long-term management of children detected in this program. Questions concerning medical aspects of the program may be directed to the following:

Cystic Fibrosis:
Accredited Cystic Fibrosis Center
University of Nebraska Medical Center CF Clinic
(402) 559-6275
John Colombo, MD, Director
Paul Sammut, MD
Heather Thomas, MD

Endocrinology Disorders:
University of Nebraska Medical Center
Pediatric Endocrinology Children's Hospital Endocrinology Clinic
(402) 955-3771
Monina Cabrera, MD
Marissa Fisher, MD
Melinda Chen, MD
Salaheddin Elrokhsi, MD
Bracha Goldsweig, MD
Zoe Gonzalez-Garcia, MD

Metabolic Disorders:
Munroe-Meyer Institute for Genetics Pediatric Metabolism
University of Nebraska Medical Center
Children's Hospital Metabolic Clinic
(402) 559-6800
Richard Lutz, MD
William Rizzo, MD

Hematologic Disorders:
UNMC and Children's Hospital
(402) 955-3950
Minnie Abromowitch, MD
Jill C. Beck, MD
Peter F. Coccia, MD
Donald W. Coulter, MD
James B. Ford, DO
Bruce G. Gordon, M.D.
James L. Harper, M.D.
Stefanie R. Lowas, MD
Harold M. Maurer, MD
Melissa A. Aquazzino, MD
Sachit A. Patel, MD
Phyllis I. Warkentin, MD

Immunologic Disorders
Children's Physicians Clinic at The Nebraska Medical Center
Children's Hospital & Medical Center
(402) 955-5570
Russell Hopp, DO
Hana Niebur, MD

Midwest Allergy and Asthma Clinic
(402) 397-7400
Ebrahim Shakir, MD