

# The Benefits of Second NBS to Detect SCID and Other T-cell Lymphopenias (TCL): A Four-Year Review in Washington State

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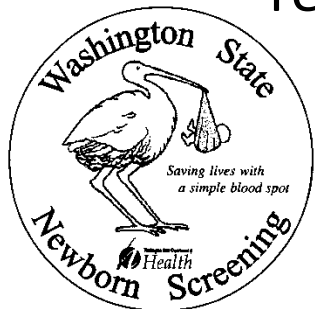
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Benjamin Peprah, Arun Singh and John Thompson, PhD

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# NBS for SCID in Washington State: Cut-off and Protocol

- ❖ SCID (TREC) screening began in WA on January 2, 2014
- ❖ Result Classification: TREC  $\geq$  81 - NORMAL  
TREC  $\leq$  80 - BORDERLINE  
TREC  $\leq$  60 - PRESUMPTIVE
- ❖ 1st NBS Presumptive  $\rightarrow$  Referral, recommend flow cytometry
- ❖ 1<sup>st</sup> NBS Borderline  $\rightarrow$  wait/request 2<sup>nd</sup> NBS
- ❖ Persistently borderline TREC on 1<sup>st</sup> & 2<sup>nd</sup> NBS  $\rightarrow$  Referral, recommend flow cytometry
- ❖ Subsequent (3<sup>rd</sup> or 4<sup>th</sup> NBS) borderline or presumptive TREC  $\rightarrow$  Referral, recommend flow cytometry



# Washington State SCID Screening Algorithm

Normal (TREC  $\geq 80$ )

Borderline  
(TREC 61 – 80)

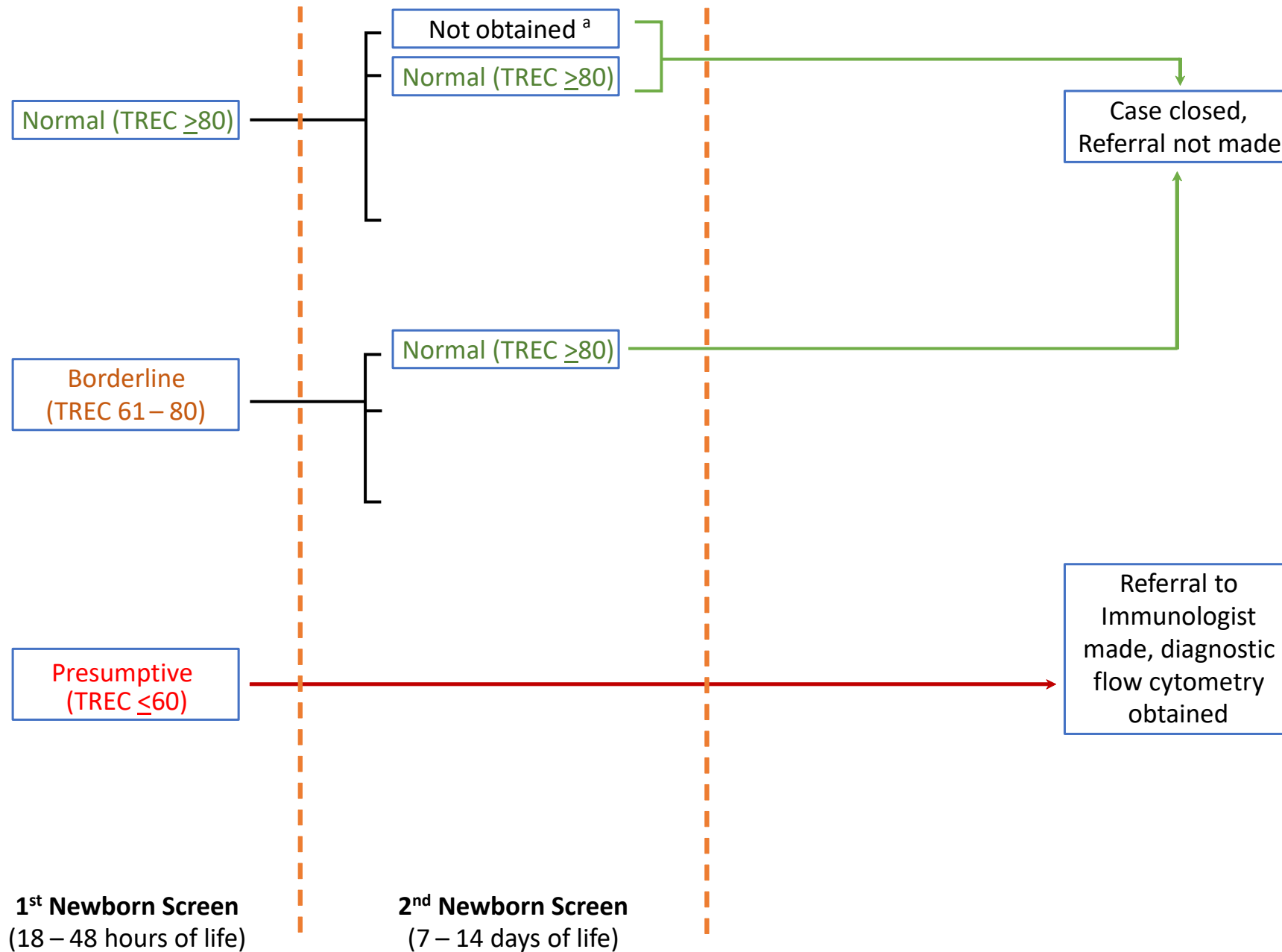
Presumptive  
(TREC  $\leq 60$ )

Referral to  
Immunologist  
made, diagnostic  
flow cytometry  
obtained

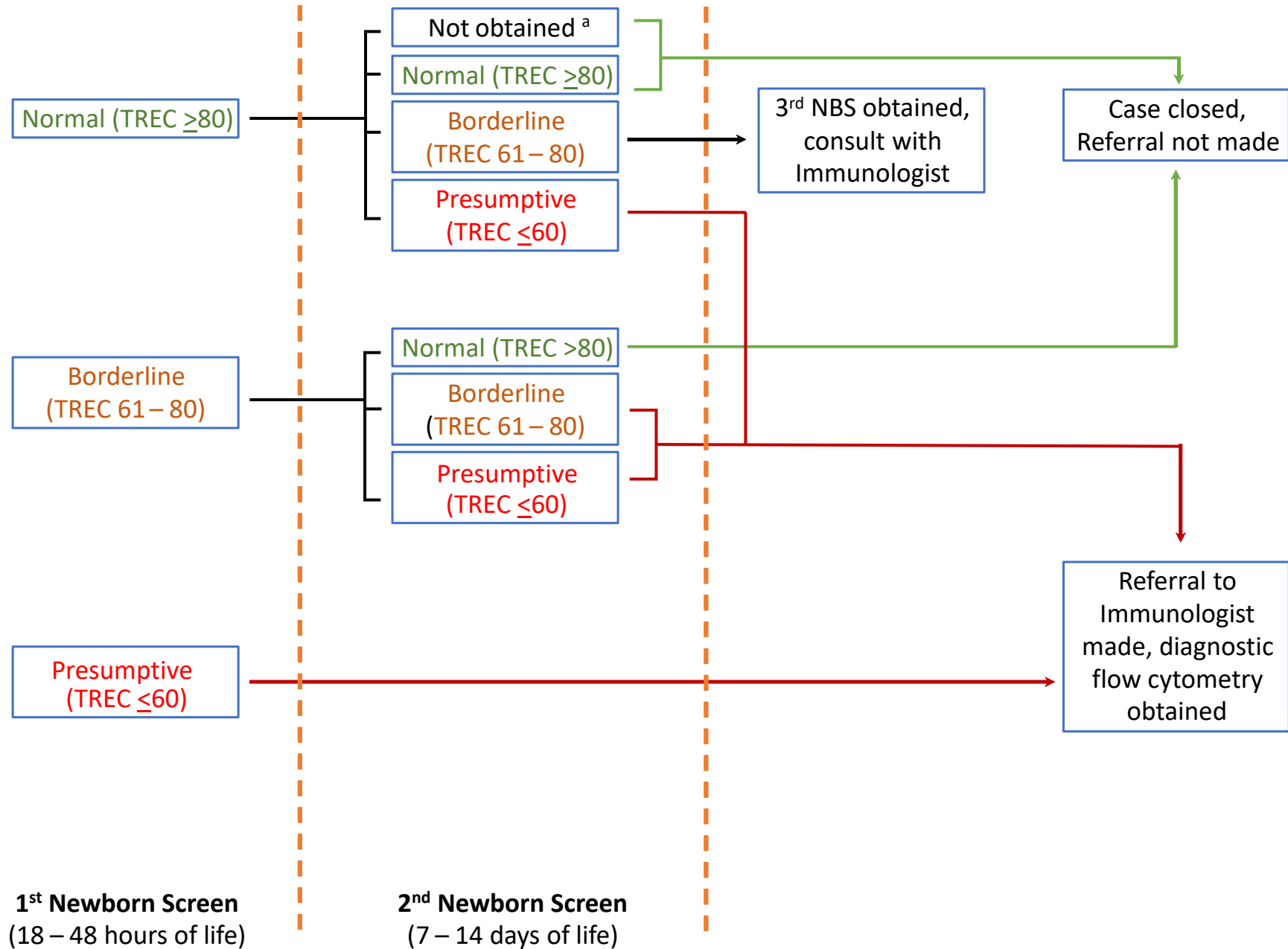
**1<sup>st</sup> Newborn Screen**  
(18 – 48 hours of life)



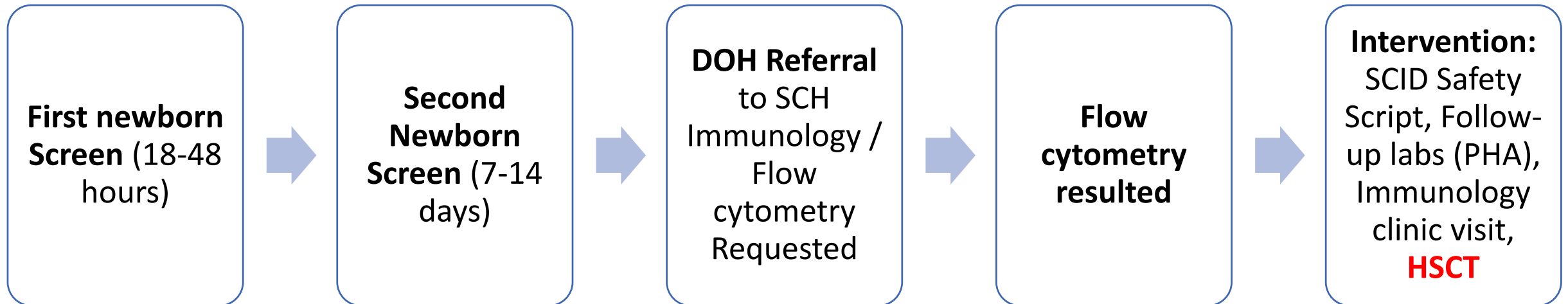
# Washington State SCID Screening Algorithm



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# Newborn Screening Timeline



# Confirmatory Testing

- Confirmatory testing sent to Seattle Children's Lab
  - Includes total WBC, differential, CD3/4/19/16/56/DR lymphocyte counts, CD4CD45RA<sup>+</sup>RO<sup>-</sup> percentage
  - Uses 1-2mL whole blood

- Interpretation:

Abnormal confirmatory screen	CD3 $\leq$ 1500 <b>and/or</b> CD4CD45RA $\leq$ 20%
Equivocal confirmatory screen	CD3 $>$ 1500 <b>and</b> CD4CD45RA $>$ 20%
False positive	CD3 $\geq$ 2500 and abnormal TREC

- ~40% of centers in US from \*PIDTC survey assess CD4CD45RA<sup>+</sup>RO<sup>-</sup> percentage


\*PIDTC – Primary Immune Deficiency Treatment Consortium

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  - Uses 1-2mL whole blood
- Interpretation:

Abnormal confirmatory screen	CD3 ≤ 1500 <b>and/or</b> CD4CD45RA ≤ 20%
Equivocal confirmatory screen	CD3 > 1500 <b>and</b> CD4CD45RA > 20%
False positive	CD3 ≥ 2500 and abnormal TREC

- ~40% of centers in US from PIDTC survey assess CD4CD45RA<sup>+</sup>RO<sup>-</sup> percentage



**Seattle Children's**  
HOSPITAL • RESEARCH • FOUNDATION

**Department of Laboratories**  
4800 Sand Point Way NE, M/S OC.8.720  
Seattle, WA 98105 (206) 987-2102  
<http://seattlechildrenslab.testcatalog.org>

FAILURE TO COMPLETE MAY DELAY RESULTS

Patient's Last Name		First	Middle	Birth date (required)	Sex
Outside Patient Number	Outside Specimen Number		Send Report To:		
Primary Care Provider:		Address:			
Provider Phone & Fax Numbers:		DIAGNOSIS / ICD-9:	Phone/Fax:		

SPECIMEN INFORMATION

Date collected: ___ / ___ / ___	Time collected: _____	Specimen Type: <input type="checkbox"/> Lavender Top/EDTA whole blood
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BILLING INFORMATION\*

\*All Samples will be billed to the referring institution unless complete billing and diagnosis information is provided when appropriate.

BILL TO: <input type="checkbox"/> Referring Institution (provide billing address if different from report address)		<input type="checkbox"/> Insurance (attach front and back copy of card)
<input type="checkbox"/> DSHS (Only Alaska, Idaho, Montana, and Washington accepted)		
Patient Address		Patient Phone
Guarantor Name	DOB	Relationship to Patient
Guarantor Address (if different from patient's)		
Guarantor Phone (if different from patient's)		Employer
Insurance Company/Medical Coverage		
Claims Address		Insurance Phone Number
Policy/ID Number	Group Number	
Subscriber Name	Subscriber DOB	

IMPORTANT INFORMATION REGARDING MEDICAL NECESSITY:

PHYSICIAN NOTIFICATION: Only tests that you believe are appropriate for patient care should be ordered. Medicare/Medicaid will pay only for tests that are medically necessary for the diagnosis and treatment of the patient, rather than for screening purposes.

NEWBORN SCREENING FOLLOW-UP TESTING for SCID

SCID NB F/U:  SCID Newborn Screen Follow-up Panel

**Specimen Requirements: 2 mL Lavender Top/EDTA whole blood. Ship overnight ambient**

If you have questions about the screening test or specimen requirements for diagnostic testing, please contact:

Seattle Children's Lab Client Services	(206) 987-2617
Sheila Weiss, MSc, Newborn Screening Program	(206) 418-5509
John D. Thompson, PhD, Newborn Screening Program	(206) 418-5531

**Results:** Please fax a copy of results to Washington State Newborn Screening Program (Fax: 206-418-5415)

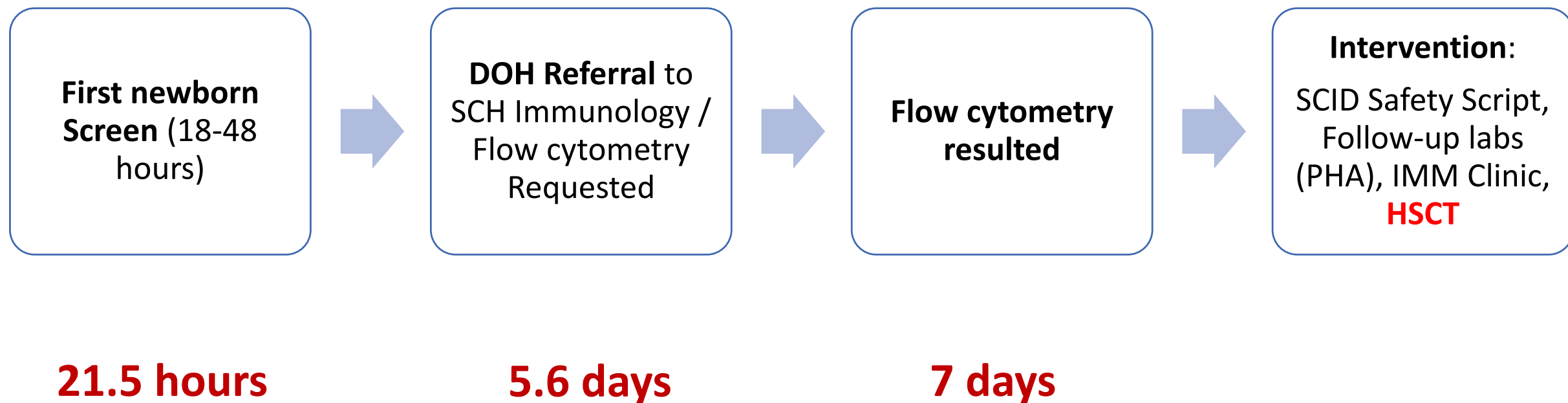
<b>Send specimens to:</b>	SEATTLE CHILDREN'S LABORATORY 4800 Sand Point Way NE, M/S: OC.8.720 Seattle, WA 98105 (206) 987-2102
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# Referrals based on sequence of NBS (2014-2017)

<b>1<sup>st</sup> NBS Referral</b>	<b>Category</b>
<b>5</b>	<b>True SCID</b>
<b>1</b>	<b>Leaky SCID</b>
<b>8</b>	<b>Idiopathic TCL</b>
<b>8</b>	<b>Syndromes with T-cell impairment</b>
<b>9</b>	<b>Secondary TCL</b>
<b>1</b>	<b>Preterm</b>
<b>10</b>	<b>False Positive</b>
<b>42</b>	<b>TOTAL</b>

# SCID/Leaky SCID Patients (2014-2017)



Average age of newborn from screening, release/reporting of results to follow-up action

# Referrals based on sequence of NBS (2014-2017)

Category	2 <sup>nd</sup> NBS Referral
True SCID	0
Leaky SCID	0
Idiopathic TCL	0
Syndromes with T-cell impairment	5
Secondary TCL	7
Preterm	0
False Positive	7
<b>TOTAL</b>	<b>19</b>

# Referrals based on sequence of NBS (2014-2017)

1 <sup>st</sup> NBS Referral	Category	2 <sup>nd</sup> NBS Referral
5	True SCID	0
1	Leaky SCID	0
8	Idiopathic TCL	0
8	Syndromes with T-cell impairment	5
9	Secondary TCL	7
1	Preterm	0
10	False Positive	7
42	TOTAL	19

# Referrals based on 3<sup>rd</sup>/4<sup>th</sup> NBS

Category	N
True SCID	0
Leaky SCID	0
Idiopathic TCL	3
Syndromes with T-cell impairment	2
Secondary TCL	6
Preterm	2
False Positive	1
<b>TOTAL</b>	<b>14</b>

# SCID and TCL: Jan 2014 to Dec 2017

Category	N
True SCID	5 (8%)
Leaky SCID	1 (1%)
TCL, no known cause (CD3: 300 - 2500) <ul style="list-style-type: none"><li>• CD3: 300-1500 (abnormal)</li><li>• CD3: 1500-2500 (equivocal)</li></ul>	11 (15%) 5 6
Syndromes with T-cell impairment	15 (20%)
Secondary TCL	22 (29%)
Preterm	3 (4%)
False Positive (CD3 $\geq$ 2500)	18 (24%)
<b>TOTAL</b>	<b>75</b>

# Total SCID Data: Jan 2014 to Dec 2017

Category	N
Positive screen or Low TREC (not referred, resolved by 2nd or subsequent NBS)	160
Cases Referred but Excluded	15

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Referrals: Based on 1 <sup>st</sup> NBS	42
Based on 2 <sup>nd</sup> NBS	19
Based on 3 <sup>rd</sup> or 4 <sup>th</sup> NBS	14
<b>TOTAL</b>	<b>75</b>
<b>True (Typical) SCID plus Leaky SCID</b>	<b>6</b>
TCL (idiopathic, secondary, syndromes)	48
Preterm	3



# Total SCID Data: Jan 2014 to Dec 2017

Category	N
Positive screen or Low TREC (not referred/resolved)	160
Cases Referred but Excluded	15
Referrals: Based on 1 <sup>st</sup> NBS	42 (56%)
Based on 2 <sup>nd</sup> NBS	19 (25%)
Based on 3 <sup>rd</sup> or 4 <sup>th</sup> NBS	14 (19%)
<b>TOTAL</b>	<b>75</b>
True (typical) SCID plus Leaky SCID	6
TCL (idiopathic, secondary, syndromes)	48
Preterm	3
False Positive (CD3 $\geq$ 2500)	18
<b>TOTAL</b>	<b>250</b>

# PPV of TREC Screen based on number of referrals

- Positive Predictive Value for SCID/Leaky SCID based on 1<sup>st</sup> NBS
  - 14.3% of referrals positive 1<sup>st</sup> NBS (TREC  $\leq$  60) had either SCID or Leaky SCID
    - 5 patients w/ SCID all had 1<sup>st</sup> TREC = 0  $\rightarrow$  11.9%
    - 1 patient w/ leaky SCID had 1<sup>st</sup> TREC = 27  $\rightarrow$  2.4%

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    - 1 patient w/ leaky SCID had 1<sup>st</sup> TREC = 27  $\rightarrow$  2.4%
- Positive Predictive Value for TCL, CD3 <2500
  - 1<sup>st</sup> NBS: 61.9%
  - 2<sup>nd</sup> NBS: 63.2%

# Washington State NBS: SCID Prevalence Rates

Year	Infants Screened	True SCID & Leaky SCID prevalence	Other TCL prevalence
2014	87,398	1:87,398	1:9,710
2015	88,367	1:88,367	1:6,311
2016	90,530	0:90,530	1:12,932
2017	87,815	1:29,271	1:4,181
<b>TOTAL</b>	<b>354,110</b>	<b>1:59,018</b>	<b>1:6,943</b>

# Abnormal/Positive Screens: Not Referred

- 160 total newborns with abnormal/borderline TREC not referred
  - 72 low birth weight (<2500g), gestational age not reported
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  - 54 normal birth weight ( $\geq 2500\text{g}$ )
    - 49% had borderline TREC 1 (61-80) with normal repeat

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    - 49% had borderline TREC 1 (61-80) with normal repeat
- Subsequent TREC (2<sup>nd</sup>-4<sup>th</sup>) which are normal can be reassuring and decrease the need for flow cytometry, thereby also minimize false positive referrals

# Conclusions

- ❖ Second NBS improves detection of non-SCID TCL → lead to delaying administration of live viral vaccines and/or starting PJP prophylaxis
- ❖ Second NBS is helpful in resolving borderline TREC in all newborns, including LBW babies



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- ❖ Second NBS is helpful in resolving borderline TREC in all newborns, including LBW babies
- ❖ First NBS is critical, facilitates timely referral, flow cytometry for patients with SCID, and leaky SCID
  - ❖ Interventions include hospitalization, cessation of breastfeeding, prophylaxis to prevent opportunistic infection, **HSCT**

# Conclusions

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- ❖ Second NBS is helpful in resolving borderline TREC in all newborns, including LBW babies
- ❖ First NBS is critical, facilitates timely referral, flow cytometry for patients with SCID, and leaky SCID
  - ❖ Interventions include hospitalization, cessation of breastfeeding, prophylaxis to prevent opportunistic infection, **HSCT**
- ❖ Persistently low TREC on 1<sup>st</sup> and 2<sup>nd</sup> NBS improves PPV for non-SCID TCL

**Thank you!**



*Washington State  
Newborn Screening*

[www.doh.wa.gov/nbs](http://www.doh.wa.gov/nbs)

(206) 418-5410  
or  
1-866-660-9050



*Washington State Department of  
Health*

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