NMC-172/23

अ० भा० आ० सं० अस्पताल/A.I.I.M.S. HOSPITAL
बहिरंग रोगी विभाग /Out Patient Department
अस्पताल के अन्दर धूम्रपान मना है।/SMOKING IS PROHIBITED IN HOSPITAL PREMISES

स्वच्छ भारत
एक कदम स्वच्छता की ओर

OPR-6

UHID: 106724089
Dept No: 2023030013154

Unit-I
Paediatric
Queue No: N13
16/05/2023

BHUDEV SHARMA
9M 9M 21D / M
S/O ANKIT KUMAR SHARMA
Add: VILL- KHAJOORWALA DIST
SAHARANPUR UTTAR PRADESH
Pin 247551 INDIA
Mob: 9760558374 New Patient General R.D Reporting 10.00 AM-11.00 AM

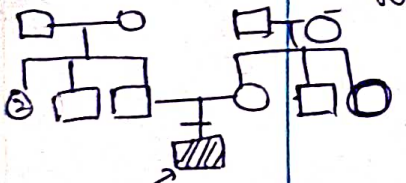
बo रो० वि० पंजीकृत सं०/O.P.D. Regn. No.

आयु Age	पता/Address
	GC :1215 FNM NMD

निदान/Diagnosis: SMA type I (SMN1 exon 7, homozygous deletion)

DOB : 26.07.2022

दिनांक/Date	उपचार/Treatment
11.4.23	9 month old male child ;
SD	Reffered from AIIMS Rishikesh
wt = 11kg (+1.77)	c/o ~~motor delay~~, weakness of all 4 limbs
lt = 74cm (+0.49)	- global dev. delay (noticed after 3 months of age)
HC = 46cm (+0.57)	- hypotonia
	↓
	- currently, neck holding ⊕, sets support ⊕ babbling ⊕
	No O2 requirement / pneumonia
	O/E Pallor 8/5
	- hypotonia ⊕
	- Absent DTR in LL
	- tongue fasciculations ⊕
	(29.4.23)
	~~Sep~~ ARMS PCR → SMN 1 gene deletion in exon 7 (homozygous) ⊕



Term/NVD/Pwt 2.8kg
CIAB/No NNU stay

अखिल भारतीय आयुर्विज्ञान संस्थान, नई दिल्ली
All India Institute Of Medical Sciences, New Delhi

UHID:	106724089	**Sex :**	Male
Patient Name :	**Mr BHUDEV SHARMA**	**Sample Received Date :**	17-May-2023 13:55 PM
Age :	9m 25d	**Department :**	Paediatrics
Lab Name:	Dept of Laboratory Medicine	**Lab Sub Centre:**	Smart Lab New OPD Block
Reg Date :	17-May-2023 13:41 PM	**Sample Collection Date:**	17-May-2023 09:16 AM
Recommended By:		**Lab Reference No:**	2312415188

Sample Details : LC1705230621 **Sample Type : Serum**

Report

BIOCHEMISTRY

Test Name *(Methodology)*	Result	UOM	Reference
Urea *(Urease/GLDH)*	27	mg/dL	17 - 49
Creatinine *(Jaffe compensated)*	**0.1**	mg/dL	0.2 - 0.4
Uric Acid *(enzymatic colorimetric)*	4.6	mg/dL	3.4 - 7.0
Calcium *(5-Nitro-5'-methyl-BAPTA)*	10.0	mg/dL	9-11
Phosphorus *(molybdate UV)*	**7.5**	mg/dL	2.5-4.5
Sodium *(Ion Selective Electrodes)*	**133**	mmol/L	135 - 145
Potassium *(Ion Selective Electrodes)*	4.5	mmol/L	3.5-5.1
Chloride *(Ion Selective Electrodes)*	101	mmol/L	98-107
Bilirubin (T) *(Colorimetric diazo)*	0.31	mg/dL	0 - 1
Bilirublin (D) *(Diazo Gen.2 Jendrassik-Grof)*	0.15	mg/dL	0 - 0.2
Bilirubin (I) *(Calculated)*	0.16	mg/dL	0 - 0.9
ALT *(IFCC without pyridoxal phosphate)*	22	U/L	0 - 57
AST *(IFCC without pyridoxal phosphate)*	29	U/L	<=40
ALP *(IFCC)*	211	U/L	122 - 469
GGT *(IFCC)*	24	U/L	8 - 61

-----End of Report-----

Dr. Sudip Kumar Datta
(Biochemistry & Immunoassay)

Dr. Tushar Sehgal
(Hematology & Coagulation)

Dr. Suneeta Meena
(Serology)

Dr Hemang (Biochemistry & Immunoassay)
17-May-2023 15:11

5/13/23, 3:43 PM Analyzer Report Plain

Central R.I.A Facility (C.R.I.A),Room No-5010
DEPARTMENT OF REPRODUCTIVE BIOLOGY
ALL INDIA INSTITUTE OF MEDICAL SCIENCES (NEW DELHI)

UHID:	106724089	**Sex :**	Male
Patient Name :	**Mr BHUDEV SHARMA**	**Sample Received Date :**	17/05/2023 12:16 PM
Age :	9 months 22 days	**Department :**	Paediatrics
Unit Name :	Unit-II	**Unit Incharge :**	
Lab Name:	Reproductive Biology	**Lab Sub Centre:**	Reproductive Biology (Main Building 2nd floor Room No.2090)
Reg Date :	16/05/2023 08:52 AM	**Sample Collection Date:**	17/05/2023 09:16 AM
Report Generated Date:	17/05/2023 04:54 pm	**Dept / IRCH No:**	20230030013164
Recommended By:		**Lab Reference No:**	216

Sample Details : RPB-170523108-I

Report

Test Name	Result	Comment	Normal Range
Troponin I	0.9 pg/mL		

Over All Comment :

Authorised Signatory
Dr.Surabhi Gupta

Verified By
sunillab

अखिल भारतीय आयुर्विज्ञान संस्थान,नई दिल्ली
ALL INDIA INSTITUTE OF MEDICAL SCIENCES, NEW DELHI

UHID:	106724089	**Sex :**	Male
Patient Name :	**Mr BHUDEV SHARMA**	**Sample Received Date :**	17/05/2023 02:47 PM
Age :	9 months 22 days	**Department :**	Paediatrics
Unit Name :	Unit-II	**Unit Incharge :**	
Lab Name:	Hematology	**Lab Sub Centre:**	Heamatology PT
Reg Date :	16/05/2023 08:52 AM	**Sample Collection Date:**	17/05/2023 09:16 AM
Report Generated Date:	17/05/2023 03:49 pm	**Dept / IRCH No:**	20230030013164
Recommended By:	Dr. Dilip SR Paeds	**Lab Reference No:**	186

Sample Details : HPT-1705230131

Report

Test Name	Result	Comment	Normal Range
PROTHROMBIN TIME(PT)	11.400 sec		9.70-12.70
INR	1.000		

Over All Comment :

Authorised Signatory

Verified By
subodajha

प्रयोगशाला कायचिकित्सा विभाग
DEPARTMENT OF LABORATORY MEDICINE
रुधिर विज्ञान
Hematology
अखिल भारतीय आयुर्विज्ञान संस्थान, अंसारी नगर, नई दिल्ली-110029
All India Institute of Medical Sciences, Ansari Nagar, New Delhi-110029

UHID:	106724089	**Sex :**	Male
Patient Name :	**Mr BHUDEV SHARMA**	**Sample Received Date :**	17/05/2023 12:25 PM
Age :	9 months 22 days	**Department :**	Paediatrics
Unit Name :	Unit-II	**Unit Incharge :**	
Lab Name:	Hematology	**Lab Sub Centre:**	Hematology (Ward)
Reg Date :	16/05/2023 08:52 AM	**Sample Collection Date:**	17/05/2023 09:16 AM
Report Generated Date:	17/05/2023 08:29 pm	**Dept / IRCH No:**	20230030013164
Recommended By:	Dr. Dilip SR Paeds	**Lab Reference No:**	386

Sample Details : HMW-1705230347

Report

Test Name	Result	Comment	Normal Range
Hb(SLS-photometry)	8.2 **g/dL**		• 11.1 - 14.1 g/dL
HCT (DirectMeasure)	33.0 **%**		• 30 - 40 %
RBC COUNT (Impedance)	5.66 **10*6/uL**		• 4.1 - 5.3 10^6/µL
T.L.C (Fluo.flowcytometry)	16.88 **10*3/uL**		• 6 - 18 10^3/µL
PLATELET COUNT (Impedance)	413 **10*3/uL**		• 200 - 550 10^3/µL
MCV (Calculated)	58.3 **fL**		• 68 - 84 fL
MCH (Calculated)	14.5 **pg**		• 24 - 30 pg
MCHC (Calculated)	24.8 **g/dL**		• 30 - 36 g/dL
RDW CV (Calculated)	25.8 **%**		• 11.6 - 14 %
NEUTRO (Fluo.flowcytometry)	31.6 **%**		• 20 - 40 %
LYMPHO (Fluo.flowcytometry)	62.8 **%**		• 37 - 73 %
MONO (Fluo.flowcytometry)	4.2 **%**		• 2 - 10 %
EOSINO (Fluo.flowcytometry)	1.0 **%**		• 1 - 4 %
BASO (Fluo.flowcytometry)	0.4 **%**		• 0 - 1 %
NUCLEATED RBC	0.0		
ABSOLUTE NEUTROPHIL COUNT (Calculated)	5.33 **10*3/uL**		• 1 - 6 10^3/µL

अ भा आ चि सं अस्पताल
A.I.I.M.S. HOSPITAL

PRESCRIPTION SLIP

25.05.2023

Name :- BHUDEV SHARMA / MALE / 11 MONTHS

UHID No. 106724089

O.P.D./Ward

Unit II Pediatrics

Rx.

Diagnosis: Spinal muscular atrophy I

Prescription for Health Authority Approval- Form 12 A Under AVXS-101 Global Managed Access Program

Name of medicine-Injection AVXS-101 (Onasemnogene Abeparavovec xioi

Dose= One Injection/ One dose

MCI-7548

डॉ. शैफाली गुलाटी / Dr. Sheffali Gulati
आचार्य / Professor
प्रभारी संभाग, बाल तंत्रिका प्रभाग
Chief, Child Neurology Division
बालरोग चिकित्सा विभाग / Department of Pediatrics
अ.भा.आ.चि.सं., नई दिल्ली / A.I.I.M.S., New Delhi-110029

Name	: MasterBHUDEV	Centre Details	:Brijlal Hospital & Research Centr
Age	: 9 Mon Sex: Male	Accession.ID	:OQG2305220027
Collection Date	: 22/May/2023 06:37PM	Referred By	:SELF
Received Date	: 22/May/2023 06:37PM	Report Date	:08/Jun/2023 04:53PM
Registration Date	: 22/May/2023	Ref. No./TRF No.	: /

DEPARTMENT OF MOLECULAR DIAGNOSTICS-III

#Spinal Muscular Atrophy (SMN1/SMN2)deletion/ duplication analysis

Whole Blood EDTA

Report Attached

***** End Of Report *****

Disclaimer: All Results released pertain to the specimen submitted to the lab
1. Test results are dependent on the quality of the sample received by the lab
2. Tests are performed as per schedule given in the test listing and in any unforeseen circumstances, report delivery may be delayed
3. Test results may show interlaboratory variations
4. All dispute and claims are subjected to local jurisdiction only. Clinical correlation advised.
5. Test results are not valid for medico legal purposes
6. For all queries, feedbacks, suggestions, and complaints, please contact customer care support +0124 665 0000

Dr. Vinay Bhatia
Ph.D.
Head- Molecular Biology
and Genomics

Dr. Shivali Ahlawat
MD. D.N.B (Path)
Head- National Reference Lab
HMC RG-No.17038

Verify this report by scanning the QR code on top. In case of any discrepancy please report to +0124 665 0000
This sample is processed at **Oncquest Laboratories Ltd.; A-17 Infocity, Sector-34, Gurugram**

Master Bhudev

CLINICAL DIAGNOSIS / SYMPTOMS / HISTORY

The patient is being evaluated for pathogenic deletions and duplications in exons 7 and 8 of *SMN1* and *SMN2* genes.

RESULTS*

PATHOGENIC VARIANT CAUSATIVE OF THE SUSPECTED PHENOTYPE WAS IDENTIFIED

Sl. No.	Genes / Exons‡	Deletions /Duplications	MLPA probe ratio (Dosage quotient)#	Copy number	Disease (OMIM)	Inheritance	Classification
1.	*SMN1* (Exon 7)	Homozygous deletion	Exon 7 (0.00)	0	Spinal muscular atrophy	Autosomal recessive	Pathogenic
2.	*SMN1* (Exon 8)	Homozygous deletion	Exon 8 (0.00)	0			
3.	*SMN2* (Exon 7)	Heterozygous duplication	Exon 7 (1.48)	3	-	-	Uncertain significance
4.	*SMN2* (Exon 8)	Heterozygous duplication	Exon 8 (1.53)	3			

ADDITIONAL FINDINGS: VARIANT(S) OF UNCERTAIN SIGNIFICANCE (VUS) IDENTIFIED

CLINICAL CORRELATION AND VARIANT INTERPRETATION

Homozygous deletion of exons 7 and 8 in the *SMN1* gene and heterozygous duplication of exons 7 and 8 in *SMN2* gene were detected within the detection limits of MLPA, in the subject (Fig.1). The subject has gene copy number ratio of *SMN1*:*SMN2* of 0:3. Functional absence of *SMN1* gene due to homozygous deletions is reported to be pathogenic in 95% of SMA cases (1). Hence, **this deletion is pathogenic and has to be carefully correlated with clinical symptoms.**

SMN2 gene copy number is of importance in SMA patients [2,3]. An increase in the number of *SMN2* copies is known to modify the phenotype leading to less severe SMA type II and III [2].

RECOMMENDATIONS

Genetic counselling is advised.

BACKGROUND

Spinal muscular atrophy (SMA) is characterized by degeneration of lower motor neurons in the spinal cord, causing progressive paralysis of the limbs and trunk, followed by muscle atrophy. SMA is one of the most frequent autosomal recessive diseases, with a carrier frequency of 1 in 38 and is the most common genetic cause of childhood mortality [4]. The phenotype is extremely variable, and patients are classified as SMA type I to III based on age at onset and clinical course. There are two (highly-similar) genes playing a pivotal role in SMA: *SMN1* and *SMN2*. These two genes can only be distinguished by single nucleotide differences in exon 7 and 8. *SMN2* is much less efficient in making the SMN protein; therefore it is the *SMN1* gene which is the determinant factor in SMA. Of these, greater than 96% are homozygous for the deletion of exons 7 and 8 of this gene. Genetic analysis for this deletion provides an efficient diagnosis for this disorder.

TEST METHODOLOGY

Copy number changes in exons 7 and 8 of the *SMN1* & *SMN2* genes were identified by hybridizing with MLPA (Multiplex Ligation-dependent Probe Amplification) probes. Each MLPA probe consists of two hemi-probes that bind to adjacent sites on the target sequence. Upon ligation and subsequent PCR amplification, each distinct MLPA probe (specific to distinct target regions) generates an amplicon with a unique length which are separated and quantified by capillary electrophoresis. Heterozygous deletions within target sequences will prevent efficient probe binding and give a 35-50% reduced relative peak area of the amplification product specific to that probe set. Copy number differences of various exons between test and control DNA samples can be detected by analyzing the MLPA peak patterns.

***Genetic test results are reported based on the recommendations of American College of Medical Genetics (Richards CS et al., Genet Med, 2015), as described below:**

Variant	A change in a gene. This could be disease causing (pathogenic) or not disease causing (benign).
Pathogenic	A disease causing variation in a gene which can explain the patients' symptoms has been detected. This usually means that a suspected disorder for which testing had been requested has been confirmed.
Likely Pathogenic	A variant which is very likely to contribute to the development of disease however, the scientific evidence is currently insufficient to prove this conclusively. Additional evidence is expected to confirm this assertion of pathogenicity.
Benign	A variant which is known not to be responsible for disease has been detected. Generally no further action is warranted on such variants when detected.
Likely Benign	A variant is not expected to have a major effect on disease however, the scientific evidence is currently insufficient to prove this conclusively. Additional evidence is expected to confirm this assertion.
Variant of Uncertain Significance	A variant has been detected, but it is difficult to classify it as either pathogenic (disease causing) or benign (non-disease causing) based on current available scientific evidence. Further testing of the patient or family members as recommended by your clinician may be needed. It is probable that their significance can be assessed only with time, subject to availability of scientific evidence.

[‡] The exon numbering is based on the *SMN1* mRNA reference sequence NM_000344.3 and *SMN2* mRNA reference sequence NM_017411.3 nomenclature respectively in the NCBI GenBank database.

[#] MLPA ratios (dosage quotient) of below 0.7 or above 1.3 are indicative of a deletion (copy number change from two to one) or duplication (copy number change from two to three), respectively. A dosage quotient of 0.0 indicates a homozygous deletion, 0.35 to 0.65 indicates heterozygous deletion, 1.35 to 1.55 indicates heterozygous duplication and 1.7 to 2.2 indicates homozygous duplication. A MLPA ratio (dosage quotient) between 0.80 to 1.20 indicates a normal copy number status

DISCLAIMER

- MLPA cannot detect any changes that lie outside the target sequence of the probes and will not detect most inversions or translocations. Even when MLPA did not detect any aberrations, the possibility remains that biological changes in that gene or chromosomal region do exist but remain undetected.
- The MLPA test will not detect the point mutations in the *SMN1* and *SMN2* genes.
- A point mutation or polymorphism in the sequence detected by a probe, which results in reduced probe binding efficiency, can also cause a reduction in relative peak area. Therefore, single exon deletions detected by MLPA should always be confirmed by other methods like multiplex PCR or sequencing.
- Note: This test is developed and validated by third party lab.

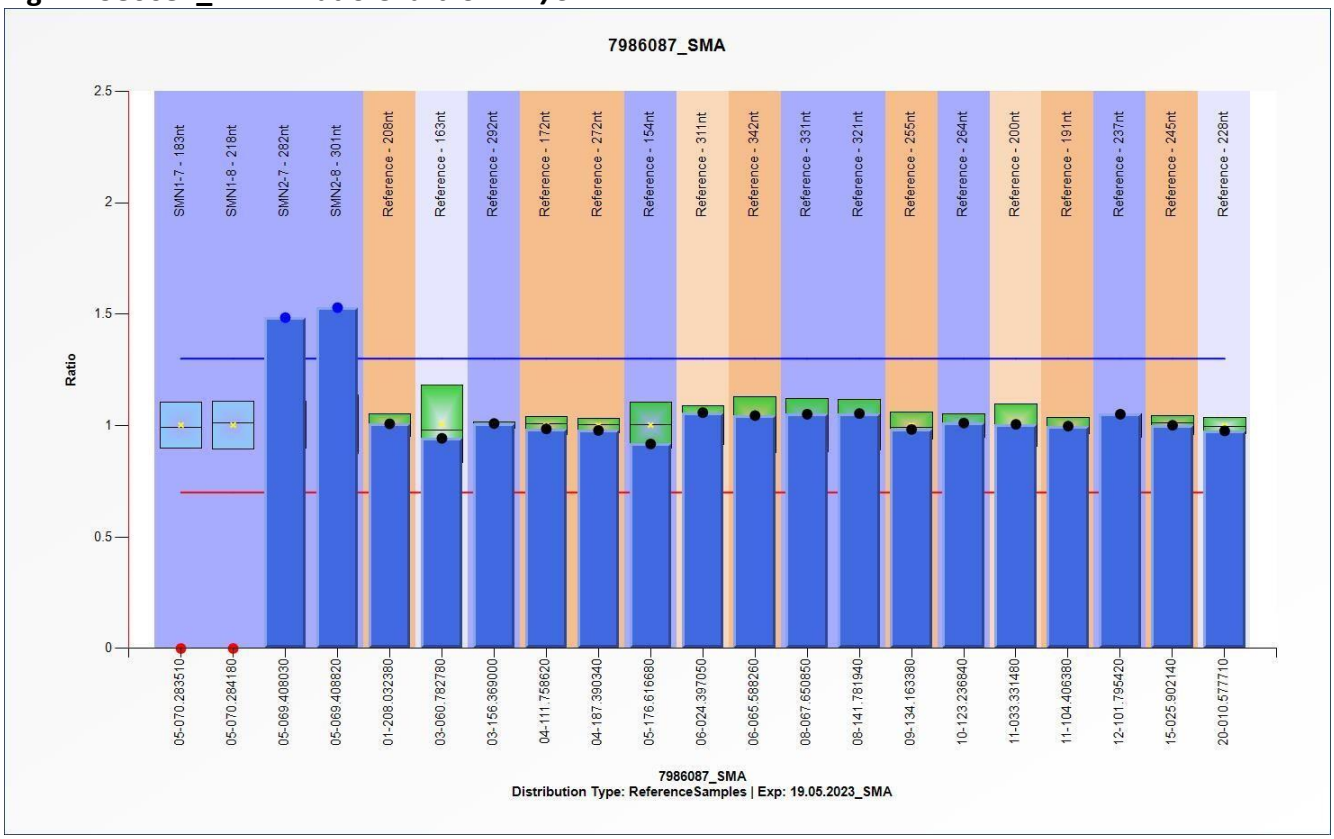
REFERENCES

1. Yoon S, Lee CH, Lee KA. Determination of *SMN1* and *SMN2* copy numbers in a Korean population using multiplex ligation-dependent probe amplification. Korean J Lab Med. 2010; 30(1):93-6.
2. Ogino S, Wilson RB. Spinal muscular atrophy: molecular genetics and diagnostics. Expert Rev Mol Diagn. 2004;4(1):15-29.
3. Prior TW et al, Homozygous *SMN1* deletions in unaffected family members and modification of the phenotype by *SMN2*. Am J Med Genet A. 2004.
4. Nilay M, Moirangthem A, Saxena D, Mandal K, Phadke SR. Carrier frequency of SMN1-related spinal muscular atrophy in north Indian population: The need for population based screening program. Am J Med Genet A. 2021 Jan;185(1):274-277. doi: 10.1002/ajmg.a.61918. Epub 2020 Oct 14. PMID: 33051992.

APPENDIX-1

SMN1/SMN2 -MLPA Result Figure

Fig.1- 7986087_MLPA Ratio Chart: *SMN1/SMN2*



APPENDIX-1

SMN1/SMN2 -MLPA Result Figure

Fig.1- 7986087_MLPA Ratio Chart: *SMN1/SMN2*

All India Institute of Medical Sciences Virbhadra Road, Rishikesh – 249201

बाल रोग विभाग
Department of Pediatrics

TO WHOMSOEVER IT MAY CONERN Date: - 16/06/2023

Sub: Prescription for Onasemnongene abeparvovee-xioi (Zolgensma) for Mr. Bhudev Sharma

Respected Sir/ madam.

This is regarding Bhudev Sharma, 10 months old boy, who has been diagnosed with a rare disorder known as Spinal muscular atrophy type I due to homozygous deletion of exon 7 and 8 in SMN1 gene with SMN2 copy number 3. Children with SMA I are not able to sit and walk independently. They can develop feeding difficulties/ respiratory complications. Child is registered in our hospital with UHID 106724089.

FDA (U.S) has approved Onasemnogene abeparvovec-xioi (Zolgensma) in May, 2019 for the treatment of S.M.A. It is an adeno-associated virus vector-based gene therapy indicated for the treatment of S.M.A. patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron / (SMN1) gene. European Medicines Agency (EMA) has also approved the drug on March, 2020.

The information on the drug as per the drug manufacturing Company are as follows:

(A) Name of the drug & Company: Onasemnogene abeparvovec xioi (Zolgensma) and Novartis.

B) Dosing schedule of the drug: 1.1×10^{14} vector genomes (vg) per kg of body weight

(c) Strength of the drug: It is a suspension for intravenous infusion, supplies as single -use vials. Zolegensma is provided in a kit containing 2 to 9 vials, as a combination of 2 vial fill volumes (either 5.5 mL or 8.3 mL.) All vials have a nominal concentration of 2.0 x 10 13 genomes (vg) per mL. Each vial of Zolgensma contains an extractable volume of not less than either 5.5 ml or 8.3 mL.

(d) With the present weight of 11 kg Bhudev Sharma would require 60.5 mL of Zolgensma (Single- dose infussion)

(e) The cost of the drug provided by the company will be approximately 2.125 million (Single dose infusion) Calculation in INR may be done based on actual exchange rates.

Though the drug has been approval by the FDA (U.S.) and EMA, the long term safety and efficacy of the drug is not proven. Studies are ongoing and results are awaited. The drug is awaiting approval by DCGI in India.

We would be happy to answer any further queries.

Sincerely

Prateek 16/06/23

Dr, Prateek Kumar Panda
Assistant Professor
Department of Pediatrics
AIIMS, Rishikesh